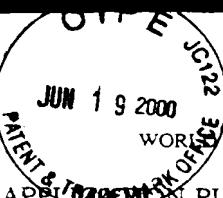


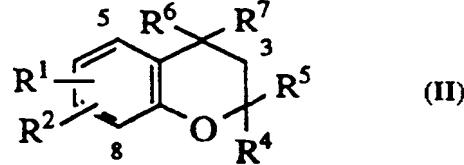
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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C07C 205/06, C07D 311/04, 279/10, 275/02, 207/00, A61K 31/555, 31/54, 31/50, 31/385, 31/35		A1	(11) International Publication Number: WO 95/30642 (43) International Publication Date: 16 November 1995 (16.11.95)
(21) International Application Number: PCT/US95/05940 (22) International Filing Date: 8 May 1995 (08.05.95)			(US). ZENG, Wenguang [CN/US]; 50 Trafalgar Court, Lawrenceville, NJ 08648 (US). LI, Ge [CN/US]; 27 Marco Polo Court, Franklin Park, NJ 08823 (US).
(30) Priority Data: 08/239,302 6 May 1994 (06.05.94)		US	(74) Agents: LOPEZ, Gabriel et al.; Pharmacopeia, Inc., 101 College Road East, Princeton, NJ 08540 (US).
(60) Parent Application or Grant (63) Related by Continuation US Filed on		Not furnished (CIP) Not furnished	(81) Designated States: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, ES, FI, GB, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LT, LU, LV, MD, MG, MN, MW, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).
(71) Applicant (for all designated States except US): PHARMA-COPEIA, INC. [US/US]; 101 College Road East, Princeton, NJ 08540 (US).			Published With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.
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(54) Title: COMBINATORIAL DIHYDROBENZOPYRAN LIBRARY



(57) Abstract

Combinatorial libraries are disclosed which are represented by the Formula (I): $(T'-L)_q-\textcircled{S}-\text{C(O)-L'-II}'$ wherein \textcircled{S} is a solid support; $T'-L-$ is an identifier residue; and $-L'-II'$ is a ligand/linker residue. These libraries contain dihydrobenzopyrans of formula (II) which interact (i.e., as agonists or antagonists) with α adrenergic receptors, dopamine receptor, σ -opiate receptors, and K^+ channels and are inhibitors of carbonic anhydrase isozymes. They are useful in the treatment of ocular diseases such as glaucoma.

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TITLE OF THE INVENTION

COMBINATORIAL DIHYDROBENZOPYRAN LIBRARY

BACKGROUND OF THE INVENTION

There is interest in methods for the synthesis of large numbers of diverse compounds which can be screened for various possible physiological or other activities. Techniques have been developed in which one adds individual units sequentially as part of the chemical synthesis to produce all or a substantial number of the possible compounds which can result from all the different choices possible at each sequential stage of the synthesis. For these techniques to be successful, it is necessary for the compounds to be amenable to methods by which one can determine the structure of the compounds so made. Brenner and Lerner (*PNAS USA* 81: 5381-83 (1992)) and WO 93/20242, for example, describe a synthesis wherein oligonucleotides are produced in parallel with and are chemically linked as genetic tags to oligopeptides as the compounds of interest. WO 93/06121 teaches methods for particle-based synthesis of random oligomers wherein identification tags on the particles are used to facilitate identification of the oligomer sequence synthesized. A detachable tagging system is described in Ohlmeyer *et al.*, *Proc. Natl. Acad. Sci. USA*, 90, 10922-10926, Dec. 1993.

SUMMARY OF THE INVENTION

The present invention relates to combinatorial chemical libraries of compounds encoded with tags and to the use of these libraries in assays to discover biologically active compounds. The present invention also relates to libraries containing dihydrobenzopyrans and using these libraries to identify biologically active members by screening for inhibition of carbonic anhydrase isozymes. The present invention also relates to members of the library which interact (i.e., as agonists or antagonists) with α adrenergic receptors, dopamine receptors, σ -opiate receptors, and K^+ channels. In particular, the present invention also relates to members of the library

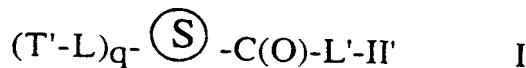


which are inhibitors of carbonic anhydrase. The invention also relates to methods for their preparation, intermediates, and to methods and pharmaceutical formulations for using these dihydrobenzopyrans in the treatment of mammals, especially humans.

5 Because of their activity as inhibitors of carbonic anhydrase isozymes, compounds of the present invention are useful in the treatment of such diseases as glaucoma.

DETAILED DESCRIPTION OF THE INVENTION

10 The combinatorial libraries of the present invention are represented by Formula I:

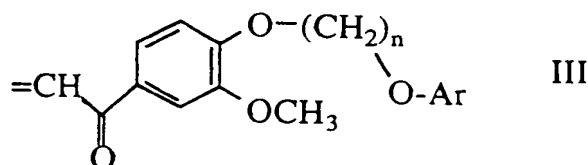


wherein:

- (S) is a solid support;
- T'-L- is an identifier residue;
- 15 -L'-II' is a ligand/linker residue; and
- q is 3-30.

Preferred compounds of Formula I are those wherein:

T'-L- is of the Formula:

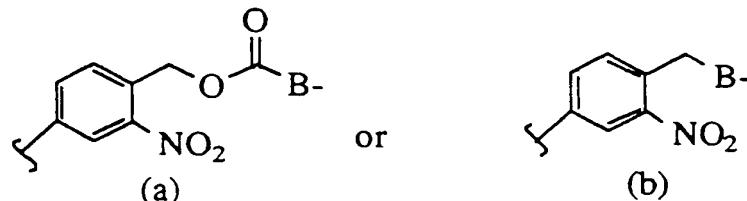


20 where n = 3-12 when Ar is pentachlorophenyl and
 n = 3-6 when Ar is 2,4,6-trichlorophenyl;
 q is 4-12; and



-3-

-L'- is



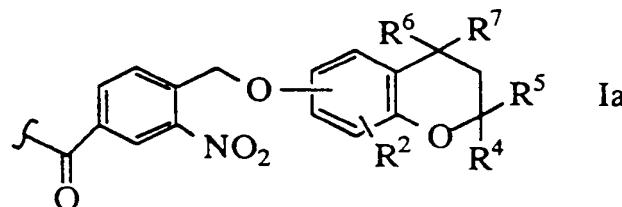
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wherein the left-hand bond as shown is the point of attachment to the solid support and the right hand bond is the point of attachment to the ligand, and B is O or $N(CH_2)_{1-6}R^{17}$, with the proviso that in (b) when B is $N(CH_2)_{1-6}R^{17}$, the ligand is attached to B through a carbonyl group.

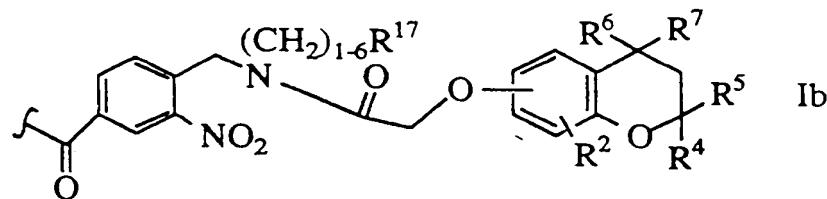
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Other preferred compounds of Formula I are those of Formulae Ia, Ib, or Ic wherein $-C(O)-L'-\Pi'$ is:

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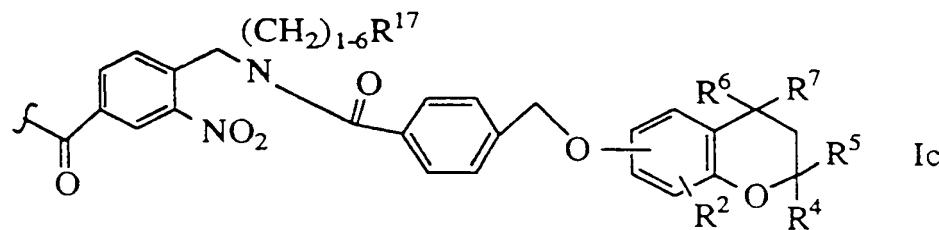
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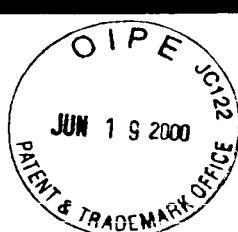


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or

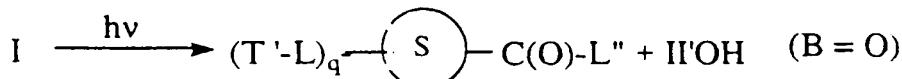
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Depending on the choice of L' (see Table 1), the ligands of Formula II may be detached by photolytic, oxidative, or other cleavage techniques. For example, when -L'- is (b) and B is O (or N(CH₂)₁₋₆R¹⁷), photolytic detachment may be represented by:



or

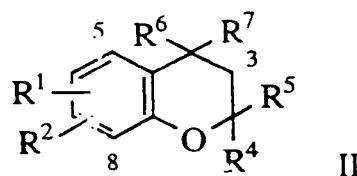
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wherein L'' is the residue from L' and H'OH (or H'NH(CH₂)₁₋₆R¹⁷) is II.

Therefore, compounds of the present invention are also represented by Formula II

10



II

wherein:

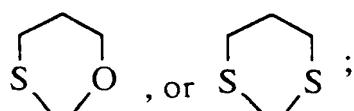
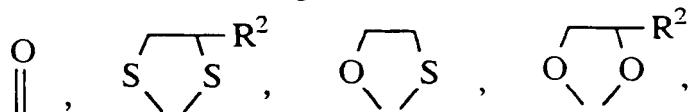
15 R¹ is OH, O(CH₂)₁₋₂OH, OCH₂CO₂H, CO₂H,
 O-Z-C(O)NH(CH₂)₁₋₆R¹⁷, or
 OCH₂-4-Phe-C(O)NH(CH₂)₁₋₆R¹⁷;

20 R² is H or lower alkyl;
 R³ is H, alkyl, aryl, or arylalkyl;
 R⁴ and R⁵ is each independently H, lower alkyl, or substituted lower alkyl where the substituents are 1-3 alkoxy, aryl, substituted aryl, carboalkoxy, carboxamido, or diloweralkylamido; or R⁴ and R⁵ taken together are -(CH₂)_n-, -(CH₂)₂-O-(CH₂)₂-, -CH₂-O-(CH₂)₃-,
 -(CH₂)₂-NR⁸-(CH₂)₂-, -CH₂-NR⁸-(CH₂)_m-,
 -(CH₂)₂CH(NHR⁸)(CH₂)₂-, -(CH₂)₂-S(O)₀₋₂-(CH₂)₂-, or
 -CH₂CH(N-loweralkyl)(CH₂)₂CHCH₂-;



-5-

one of R⁶ and R⁷ is H and the other is H, OH, or N(CH₂)₁₋₆R¹⁴R¹⁵; or R⁶ and R⁷ taken together are



R⁸ is
5 lower alkyl, aryl lower alkyl, heteroaryl, or heteroaryl lower alkyl, wherein aryl is optionally substituted with 1-3 substituents selected from lower alkyl, lower alkoxy, halo, CN, NH₂, COOH, CONH₂, carboalkoxy, and mono- or di-lower alkylamino and wherein heteroaryl is a mono- or
10 bicyclic heteroaromatic ring system of 5 to 10 members including 1 to 3 heteroatoms selected from O, N, and S and 0-3 substituents selected from halo, amino, cyano, lower alkyl, carboalkoxy, CONH₂, and S-lower alkyl;
R⁹ is
15 lower alkyl, aryl, aryl lower alkyl, heteroaryl, aryl substituted by 1-3 substituents selected from alkyl, alkenyl, alkoxy, methylene dioxy, and halo, or a 5 to 6-membered heterocyclic ring wherein the hetero atom is O or N, wherein heteroaryl is a heteroaromatic ring of 5 to 6 members including 1 to 2 heteroatoms selected from O, N, and S and 0-2 substituents selected from lower alkyl, dialkylamino, lower alkoxy, and halo;
R¹⁰ and R¹¹ is each independently lower alkyl, aryl, aryl lower alkyl, or aryl substituted by 1-3 substituents selected from lower alkyl, halo, alkoxy, and haloalkyl;
20 R¹² is lower alkyl, aryl, heteroaryl, aryl lower alkyl, heteroaryl lower alkyl, a 5- or 6-membered heterocyclic ring containing 1-2 heteroatoms selected from O, S, and N, a 5- or 6-membered heterocyclic ring containing 1-2 heteroatoms selected from O, S, and N lower alkyl, or aryl substituted with 1-3 substituents selected from lower
25
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-6-

alkyl, alkoxy, halo, sulfamoyl, lower alkyl sulfamoyl, cyano, and phenyl;

10 R¹³ is lower alkyl, aryl, or aryl substituted with 1-3 substituents selected from lower alkyl, alkoxy, halo, CN, and haloalkyl; H; alkyl substituted by 1-3 alkoxy, S-loweralkyl, sulfamoyl, halo, alkylsulphonamido, or arylsulphonamido; alkenyl; alkynyl; aryl; substituted aryl; heteroaryl; substituted heteroaryl; heterocycloalkyl; -CH₂NR¹⁶C(O)R¹⁶; -C(O)NR¹⁶R¹⁶; -CH₂OC(O)R¹⁶; or -CH₂SC(O)R¹⁶;

15 R¹⁵ is H, alkyl, -C(O)X, -C(S)X, or -C(NCN)NR³R³; R¹⁶ is lower alkyl, substituted lower alkyl, aryl, or substituted aryl;

20 R¹⁷ is H; alkyl substituted by 1-3 alkoxy, S-loweralkyl, sulfamoyl, halo, alkylsulphonamido, or arylsulphonamido; alkenyl; alkynyl; aryl; substituted aryl; heteroaryl; substituted heteroaryl; heterocycloalkyl; -CH₂NR¹⁶C(O)R¹⁶; -C(O)NR¹⁶R¹⁶; -CH₂OC(O)R¹⁶; or -CH₂SC(O)R¹⁶;

25 X is alkyl, aryl, arylalkyl, O-loweralkyl, or NR³R³
Z is -(CH₂)₁₋₆, optionally substituted with 1-3 lower alkyl; CHR²; Phe-CH₂-; where Phe is optionally mono-substituted with halogen, lower alkyl, or alkoxy; or heteroarylene-(CH₂)-;

30 m is 2 or 3;
n is 4-9;
or a pharmaceutically acceptable salt thereof.

Preferred compounds of Formula II are those wherein R¹² is sulfamoylphenyl, most preferably p-sulfamoylphenyl.

30 A preferred embodiment of the invention is a compound of Formula II wherein:

R¹ is OH, OCH₂C(O)NH(CH₂)₁₋₆R¹⁴, or OCH₂-4-Phe-C(O)NH(CH₂)₁₋₆R¹⁴;

R² is H or lower alkyl;



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R⁴ and R⁵ is each lower alkyl; or R⁴ and R⁵ taken together are -(CH₂)₅-, -(CH₂)₂-O-(CH₂)₂-, -(CH₂)₂-NR⁸-(CH₂)₂-, -(CH₂)₂-CH(NHR⁸)(CH₂)₂-, -(CH₂)₂-S-(CH₂)₂-, or
-CH₂CH(NCH₃)(CH₂)₂CHCH₂-;

5 R⁶/R⁷ are H/OH, =O, or -S(CH₂)₂S-; R⁸ is H, COOR⁹, CONHR¹⁰, CSNHR¹¹, COR¹², SO₂R¹³, .

10 lower alkyl, aryl lower alkyl, heteroaryl wherein the ring members include 1 to 3 N atoms and the substituents are halo or amino, heteroaryl lower alkyl wherein heteroaryl is 6-membered and the heteroatoms are N, or aryl lower alkyl substituted with 1 substituent selected from lower alkyl, alkoxy, and halo;

15 R⁹ is lower alkyl, aryl lower alkyl, aryl, tetrahydrofuryl, tetrahydropyranyl, or aryl substituted by 1 to 2 substituents selected from lower alkyl, alkenyl, alkoxy, methylene dioxy, and halo;

R¹⁰ and R¹¹ is each independently aryl, aryl lower alkyl, or aryl substituted by 1 substituent selected from lower alkyl, halo, alkoxy, trifluoromethyl, and pentafluoroethyl;

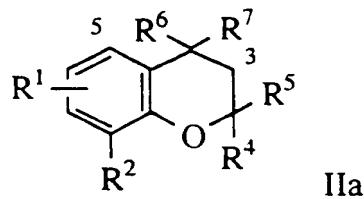
20 R¹² is lower alkyl, aryl, aryl lower alkyl, heteroaryl lower alkyl wherein the heteroatoms are N, a 5- or 6-membered heterocyclic ring containing 1-2 heteroatoms selected from S and N lower alkyl, or aryl substituted with 1 substituent selected from lower alkyl, alkoxy, halo, sulfamoyl, cyano, or phenyl;

25 R¹³ is lower alkyl, aryl, or aryl substituted with 1 substituent selected from lower alkyl, alkoxy, and halo; or a pharmaceutically acceptable salt thereof.

30 Most preferred compounds of the invention are represented by the formula:



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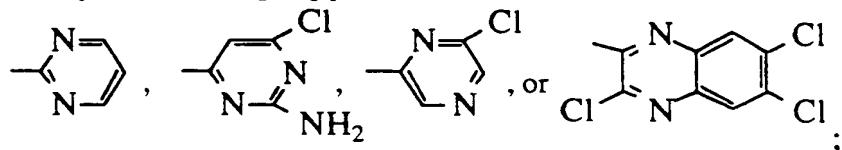
wherein:

R¹ is 6- or 7-OH;R² is H or lower alkyl;

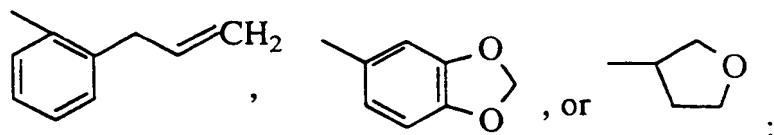
5 R⁴ and R⁵ is each methyl; or R⁴ and R⁵ taken together are -(CH₂)₅-,
 -(CH₂)₂-O-(CH₂)₂- , -(CH₂)₂-NR⁸-(CH₂)₂-,
 -CH₂-NR⁸-(CH₂)₃- , -CH₂-NR⁸-(CH₂)₂- , or
 -(CH₂)₂-CH(NHR⁸)(CH₂)₂-;

10 one of R⁶ and R⁷ is H and the other is OH or R⁶ and R⁷ taken together
 are =O or -S(CH₂)₂S-;

R⁸ is H, COOR⁹, CONHR¹⁰, CSNHR¹¹, COR¹², SO₂R¹³,
 benzyl, -CH₂-Ph-4-F, -CH₂-Ph-4-OCH₃, -CH₂-4-Py,
 n-butyl, -CH₂-c-propyl,

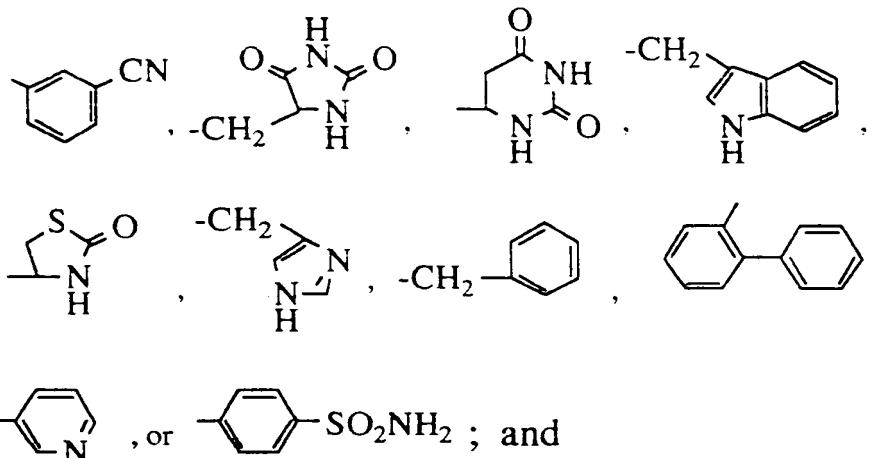


15 R⁹ is i-propyl, phenyl, phenethyl, t-butyl,

R¹⁰ is phenyl, p-chlorophenyl, or p-trifluoromethylphenyl;R¹¹ is phenyl, benzyl, or 1-naphthyl;



R^{12} is



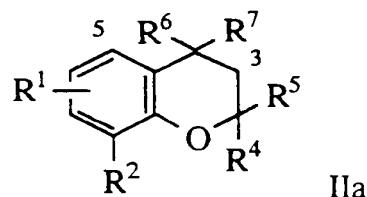
R¹³ is

1- or 2-naphthyl, phenyl, 4-chlorophenyl, 4-

methylphenyl, 4-t-butylphenyl, n-butyl, or i-propyl;

5 or a pharmaceutically acceptable salt thereof.

Most preferred compounds of the invention are also represented by the formula:



wherein:

10 R¹ is 6- or 7-OH when R² is H;
 R¹ is 7-OH when R² is CH₃;
 R⁴ and R⁵ is each methyl; or R⁴ and R⁵ taken together are -(CH₂)₅-,
 -(CH₂)₂-O-(CH₂)₂- , -(CH₂)₂-NR⁸-(CH₂)₂- ,
 -CH₂-NR⁸-(CH₂)₃- , -CH₂-NR⁸-(CH₂)₂- , or -(CH₂)₂-
 CH(NHR⁸)(CH₂)₂- ;
 one of R⁶ and R⁷ is H and the other is OH or R⁶ and R⁷ taken together
 are =O or -S(CH₂)₂S-; and
 R⁸ is

-10-



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<chem>CN(C)C(=O)c1ccccc1</chem>	<chem>CN1C=CC2=C1C(=O)SC2</chem>	<chem>CCCS(=O)(=O)C</chem>
5 <chem>Clc1ccccc1N(C)C(=O)C</chem>	<chem>Cc1ccccc1C(=O)C</chem>	<chem>CC(C)CSC(=O)(=O)C</chem>
10 <chem>FC(F)(F)c1ccccc1N(C)C(=O)C</chem>	<chem>Cc1ccccc1C(=O)c2ccccc2</chem>	<chem>CC(C)(C)c1ccccc1SC(=O)(=O)C</chem>
15 <chem>C#Nc1ccncc1</chem>	<chem>CCc1ccccc1OC</chem>	<chem>CCN(c1nc(Cl)cncc1)C</chem>
20 <chem>c1ccccc1Cc2cc(Cl)c3cc(Cl)cnc3c2</chem>	<chem>CCCCC(C)C</chem>	<chem>FCc1ccccc1</chem>
25 <chem>C#C</chem>	<chem>CC(C)(C)OC(=O)C</chem>	or H.

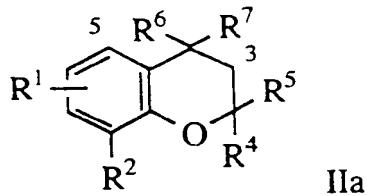
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-12-

Most preferred compounds of the invention are represented by the formula:



IIa

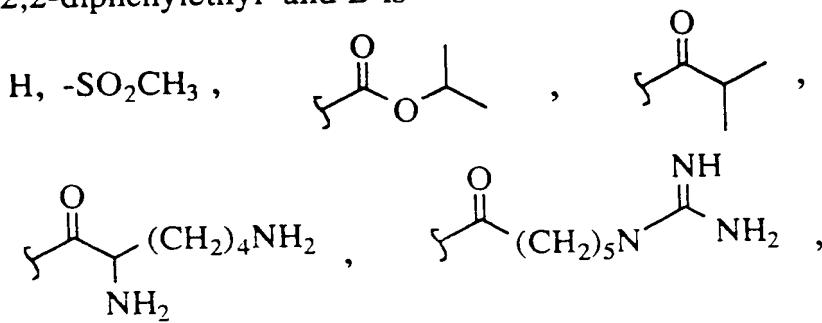
wherein:

5 R¹ is 6- or 7-OCH₂C(O)NH(CH₂)₁₋₆R¹⁷, or 6- or 7-OCH₂-4-Phe-C(O)NH(CH₂)₁₋₆R¹⁷ when R² is H;

 R¹ is 7-OCH₂C(O)NH(CH₂)₁₋₆R¹⁷, or 7-OCH₂-4-Phe-C(O)NH(CH₂)₁₋₆R¹⁷ when R² is CH₃;

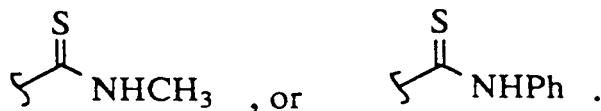
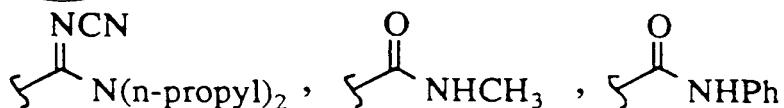
10 R⁴ and R⁵ is each methyl; or R⁴ and R⁵ taken together are -(CH₂)₅-, -(CH₂)₂-O-(CH₂)₂-, -(CH₂)₂-NR⁸-(CH₂)₂-, -(CH₂)₂-CH(NHR⁸)(CH₂)₂-, -(CH₂)₂-S-(CH₂)₂-, or
 -CH₂CH(NCH₃)(CH₂)₂CHCH₂-,

15 or R⁴ is methyl and R⁵ is CH₂OCH₃ or -(CH₂)₃N(Et)₂;
one of R⁶ and R⁷ is H and the other is OH; or R⁶ and R⁷ taken together
15 are =O or -S(CH₂)₂S-; or one of R⁶ and R⁷ is H and the
other is NAB, where A is methyl, 2-methoxyethyl,
2-phenylethyl, 4-methoxybenzyl, 2-tetrahydro-
furylmethyl, 2(3,4-dimethoxyphenyl)ethyl, or
2,2-diphenylethyl and B is



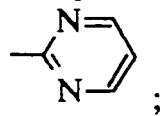


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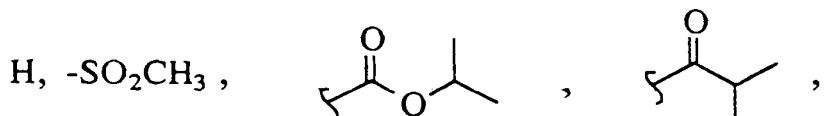
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R^8 is H, CONHCH₃, SO₂Ph, (CH₂)₃CH₃, CO(CH₂)₂CH₃, benzyl, -C(O)-(4-Phe)-SO₂NH₂, or

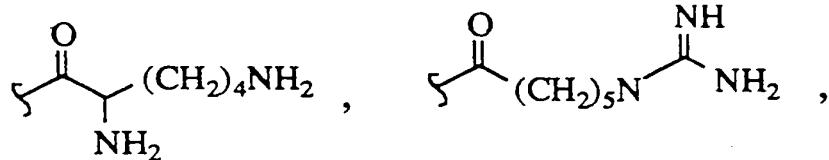


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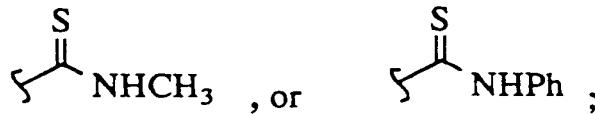
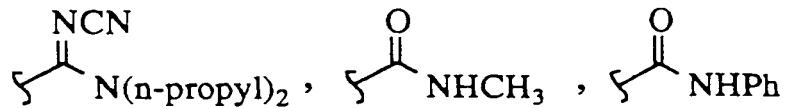
R^{13} is



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25 $(\text{CH}_2)_{1-6}\text{R}^{14}$ is methyl, n-butyl, 3-methoxy-n-propyl, CH₂-c-propyl, or -(CH₂)₁₋₃-phenyl; and

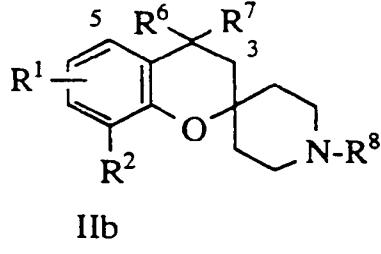
$(\text{CH}_2)_{1-6}\text{R}^{17}$ is methyl, 2-methoxyethyl, 2-phenylethyl, 4-methoxybenzyl, methyl-2-tetrahydrofuryl, 2(3,4-dimethoxyphenyl)ethyl, or 2,2-diphenylethyl;

30 or a pharmaceutically acceptable salt thereof.

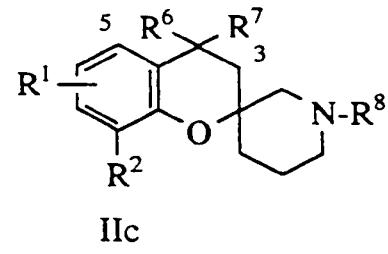


Especially preferred, as inhibitors of carbonic anhydrase, are compounds of formulae IIb, IIc, and IId:

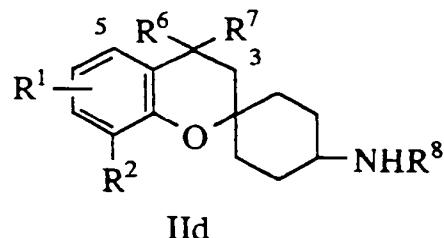
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wherein:

15 R^1 is 6- or 7-OH, 6- or 7-OCH₂C(O)NH(CH₂)₁₋₆R¹⁷, or
 6- or 7-OCH₂-4-Phe-C(O)NH(CH₂)₁₋₆R¹⁷;

R^2 is H or CH₃;

R^8 is -CO-Ph-p-SO₂NH₂; and

R^6 and R^7 together are =O or -SCH₂CH₂S-.

Most preferred of these are the following compounds:

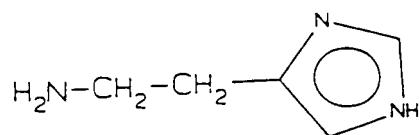
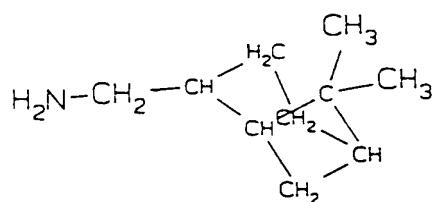
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	Formula IIb	Formula IIc	Formula IIId		
R^1	7-OH	6-OH	6-OH	6-OH	7-OH
R^2	H	H	H	H	CH ₃
R^6/R^7	-O-	-SCH ₂ CH ₂ S-	-O-	-SCH ₂ CH ₂ S-	-SCH ₂ CH ₂ S-

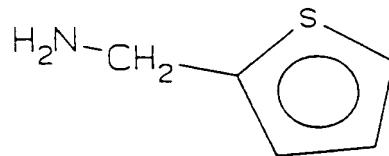
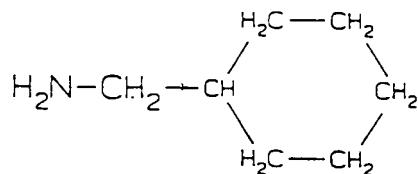
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R^{14} and R^{17} may each be any pharmacologically relevant organic radical, such as those derived by removal of H₂NCH₂- from the following compounds:

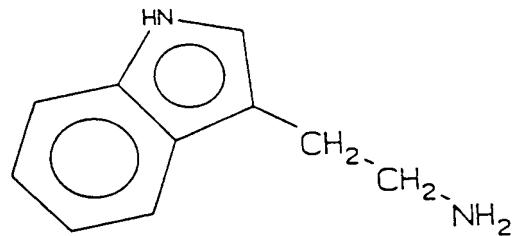
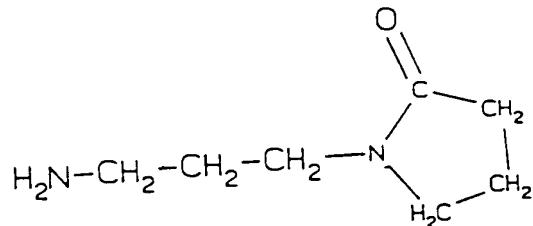
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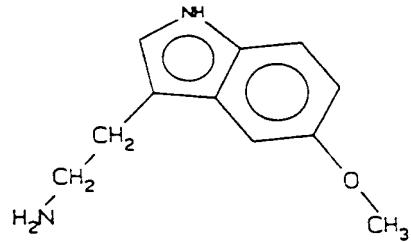
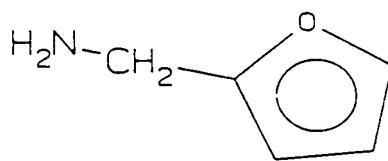
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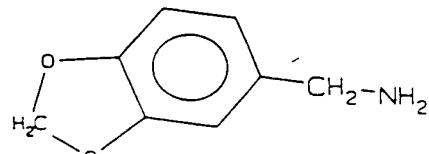
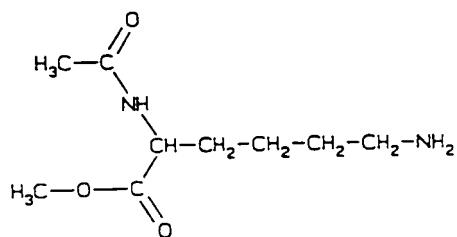
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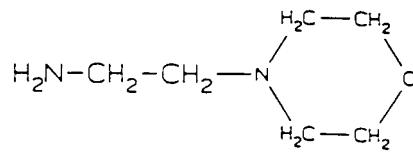
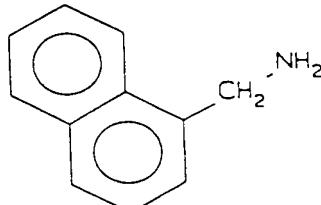
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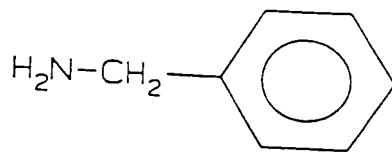
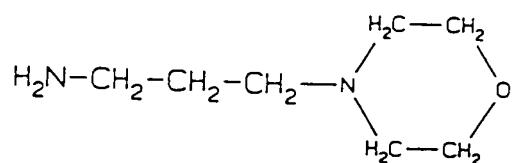
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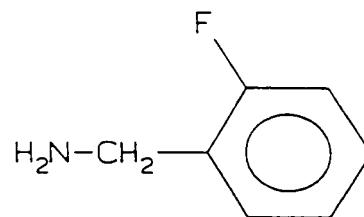
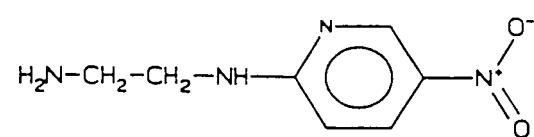
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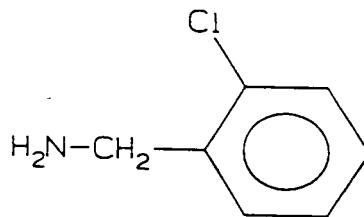
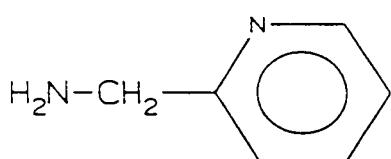
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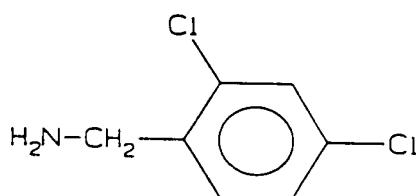
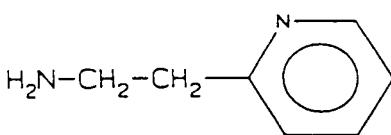
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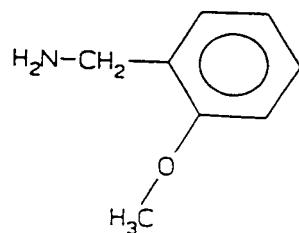
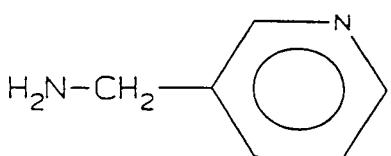
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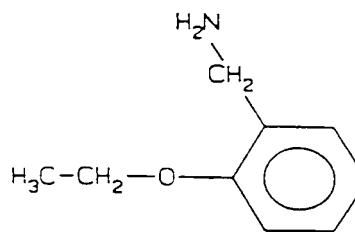
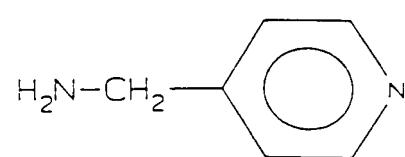
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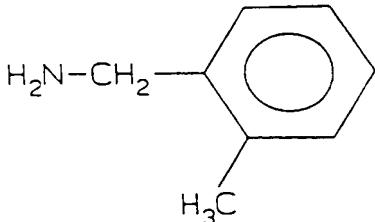
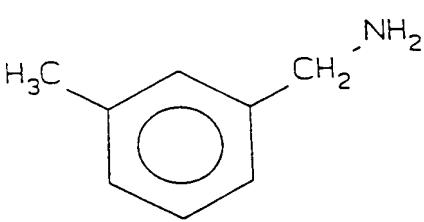
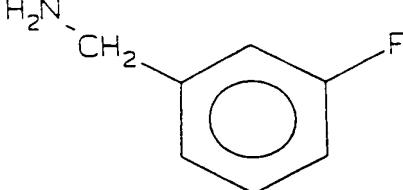
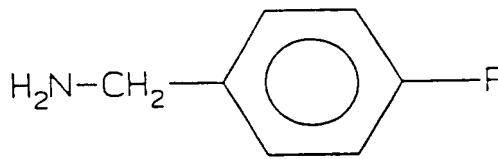
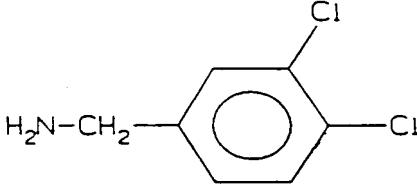
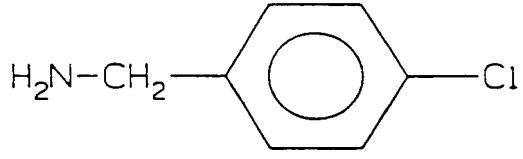
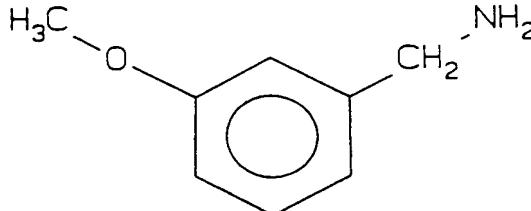
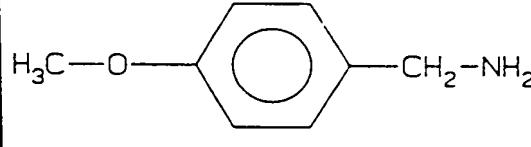
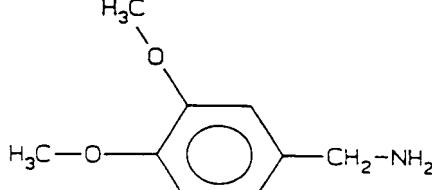
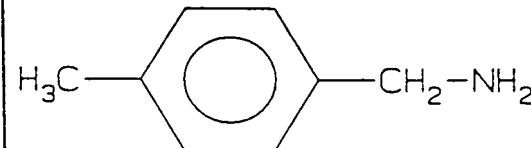
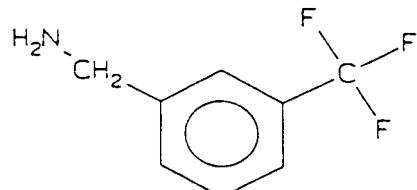
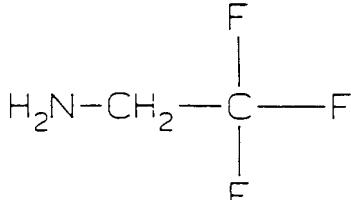
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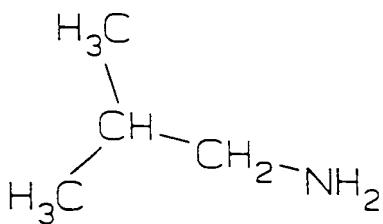
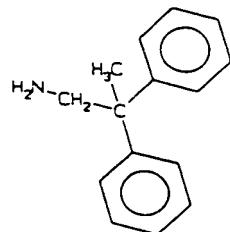
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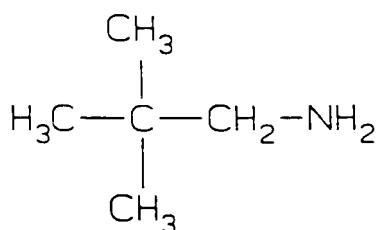
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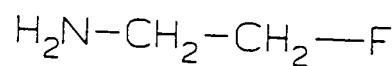
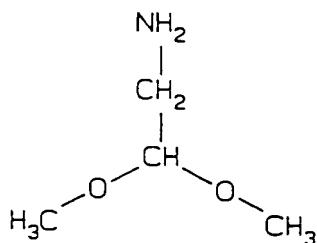
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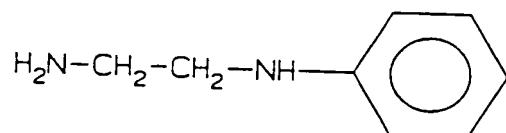
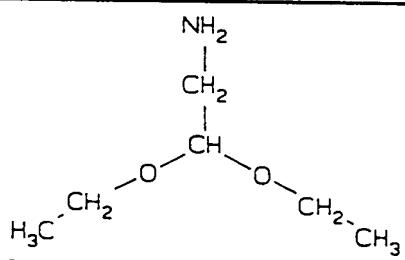
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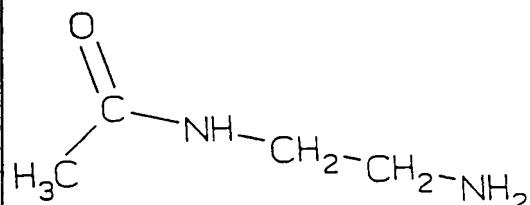
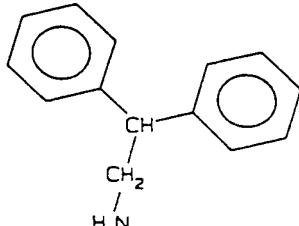
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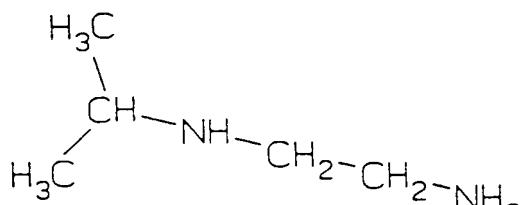
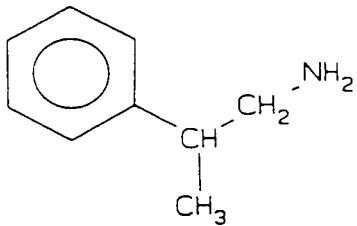
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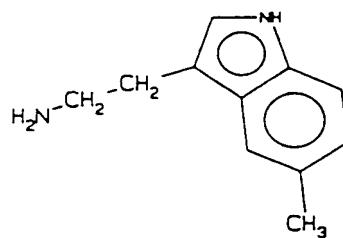
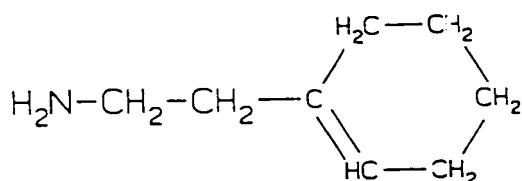
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10	$\text{H}_2\text{N}-\text{CH}_2-\text{CH}=\text{CH}_2$	$\text{H}_3\text{C}-\text{CH}_2-\text{O}-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{NH}_2$
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-21-

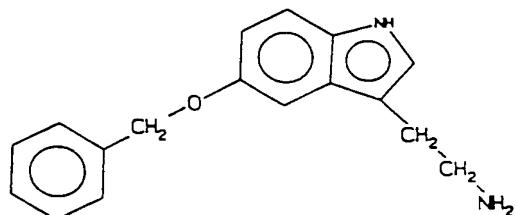
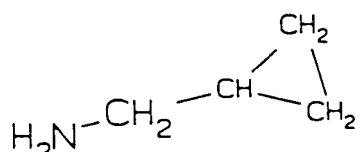
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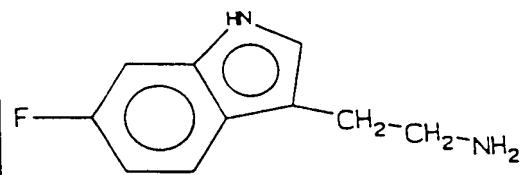
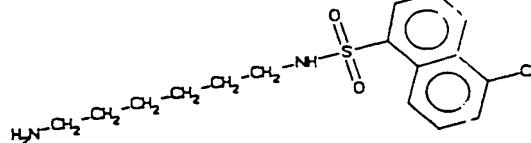
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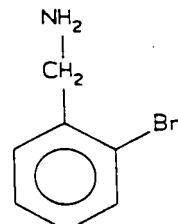
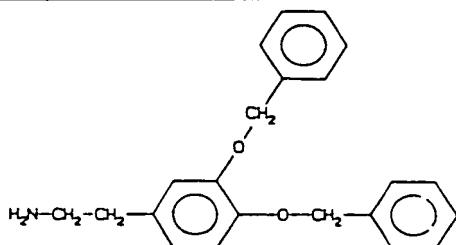
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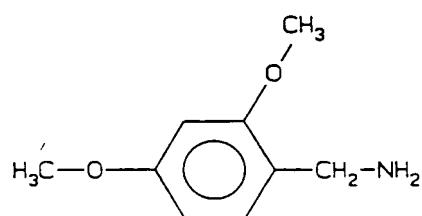
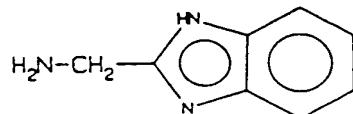
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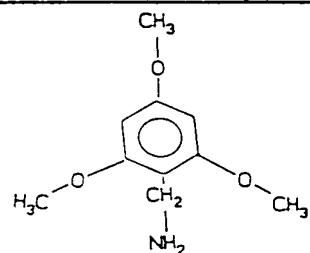
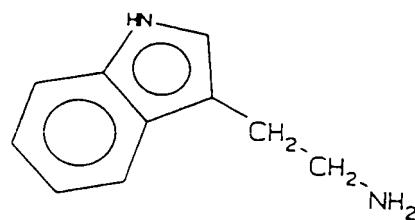
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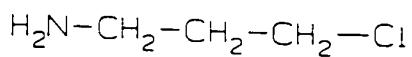
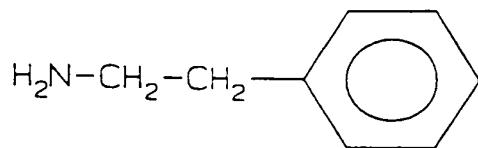


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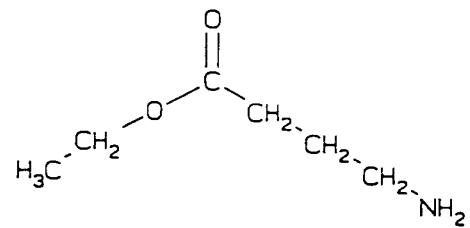
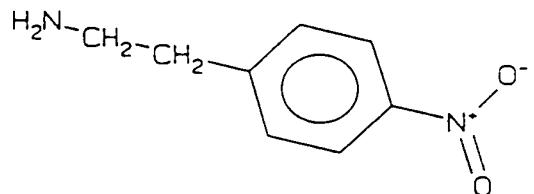
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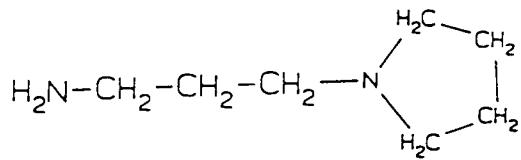
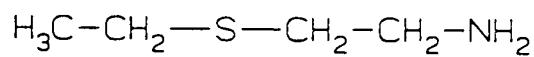
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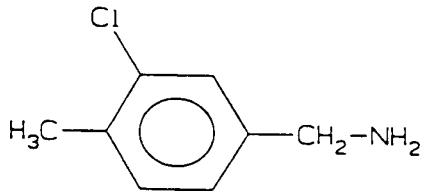
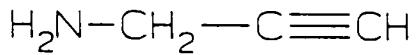
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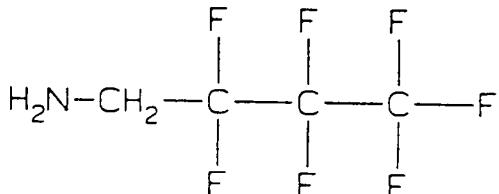
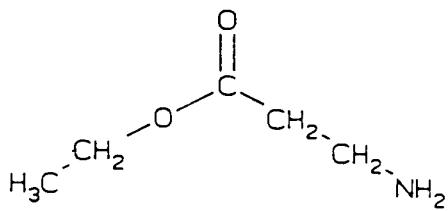
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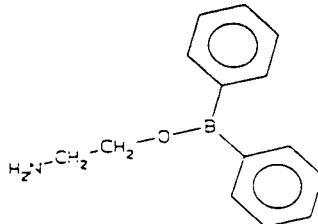
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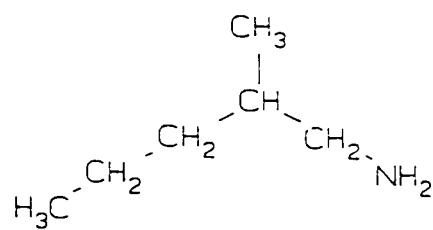
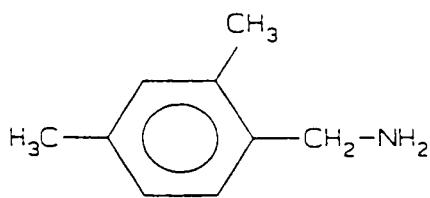
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$\text{H}_3\text{C}-\text{S}-\text{CH}_2-\text{CH}_2-\text{NH}_2$	
$\text{H}_3\text{C}-\text{CH}_2-\text{S}-\text{CH}_2-\text{CH}_2-\text{NH}_2$	$\text{H}_2\text{N}-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}(\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2)-\text{NH}_2$
$\text{H}_3\text{C}-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{S}-\text{CH}_2-\text{CH}_2-\text{NH}_2$	
$\text{H}_3\text{C}-\text{O}-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{NH}_2$	$\text{H}_2\text{N}-\text{CH}_2-\text{CH}(\text{CH}_2-\text{CH}_2-\text{O}-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{NH}_2)$
$\text{H}_3\text{C}-\text{O}-\text{CH}_2-\text{CH}_2-\text{O}-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{NH}_2$	

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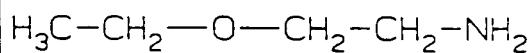
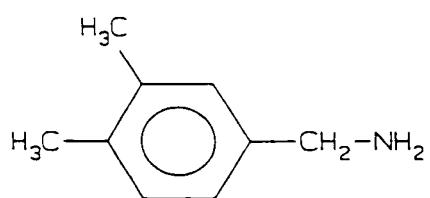
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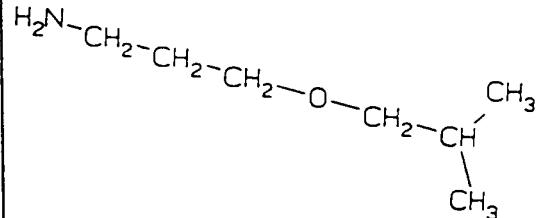
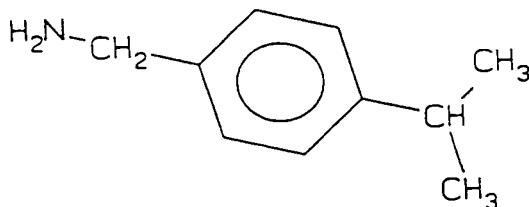
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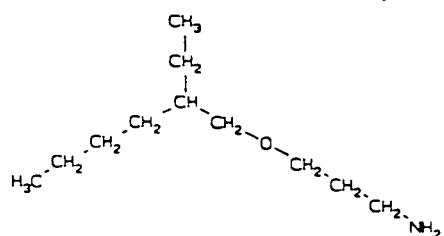
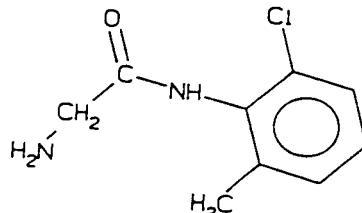
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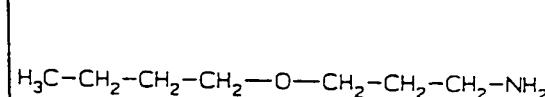
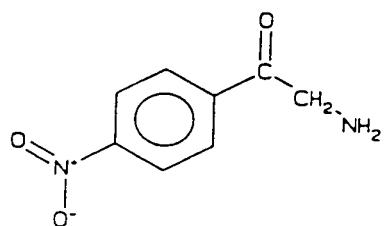
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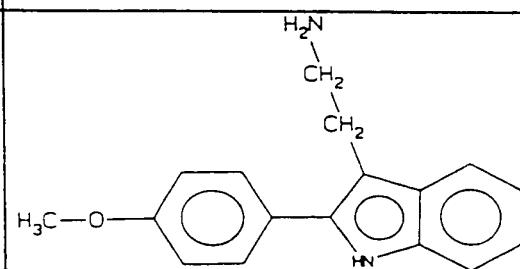
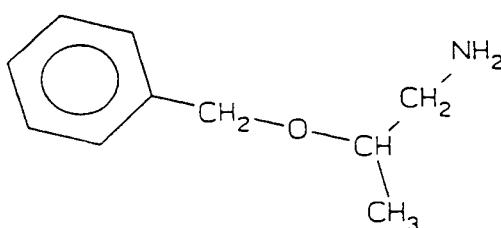
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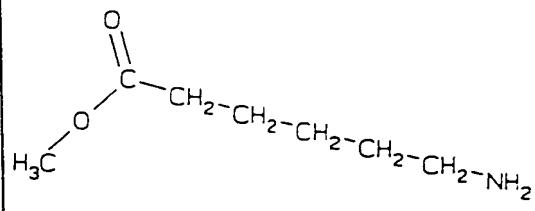
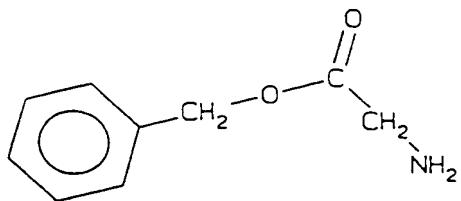


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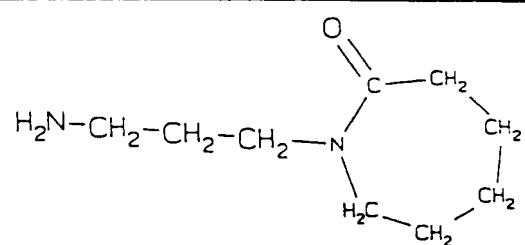
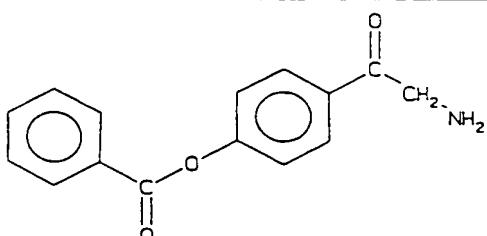




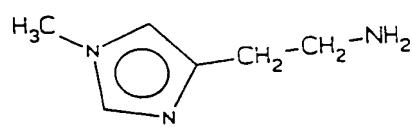
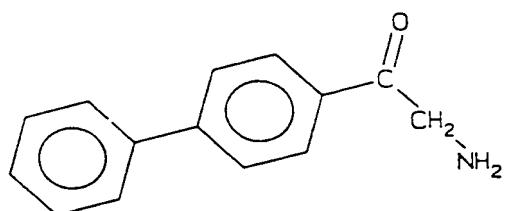
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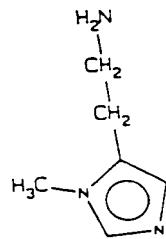
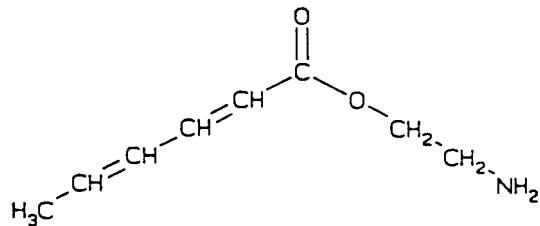
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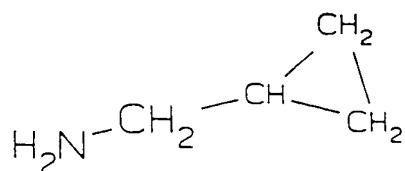
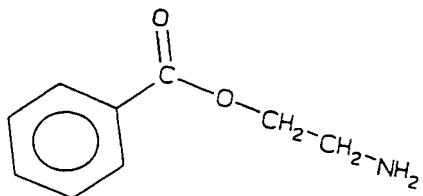
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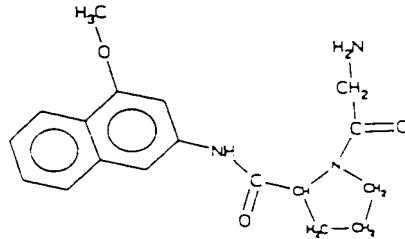
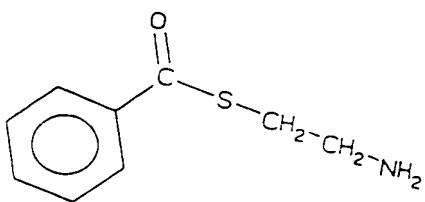
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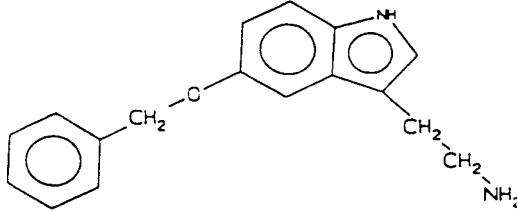
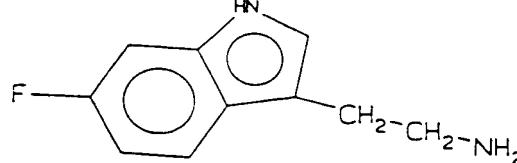
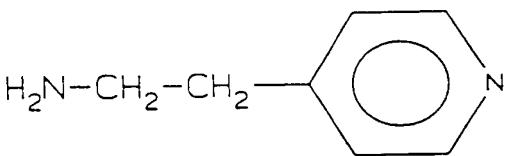
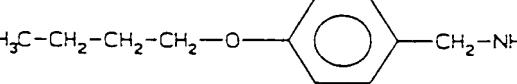
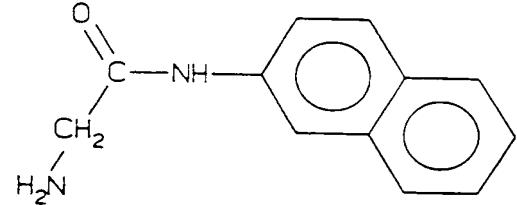
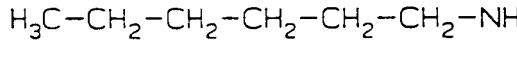
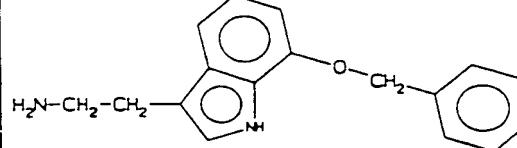
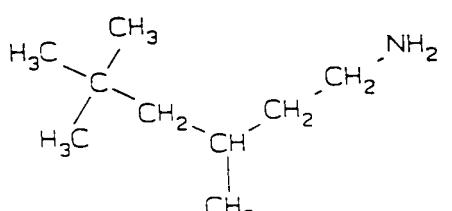
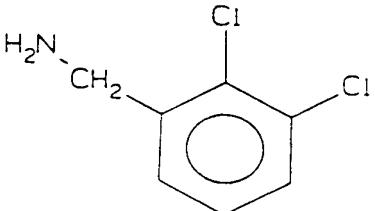
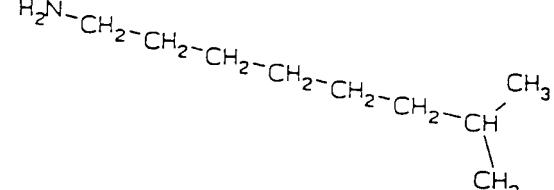
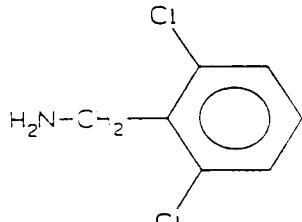
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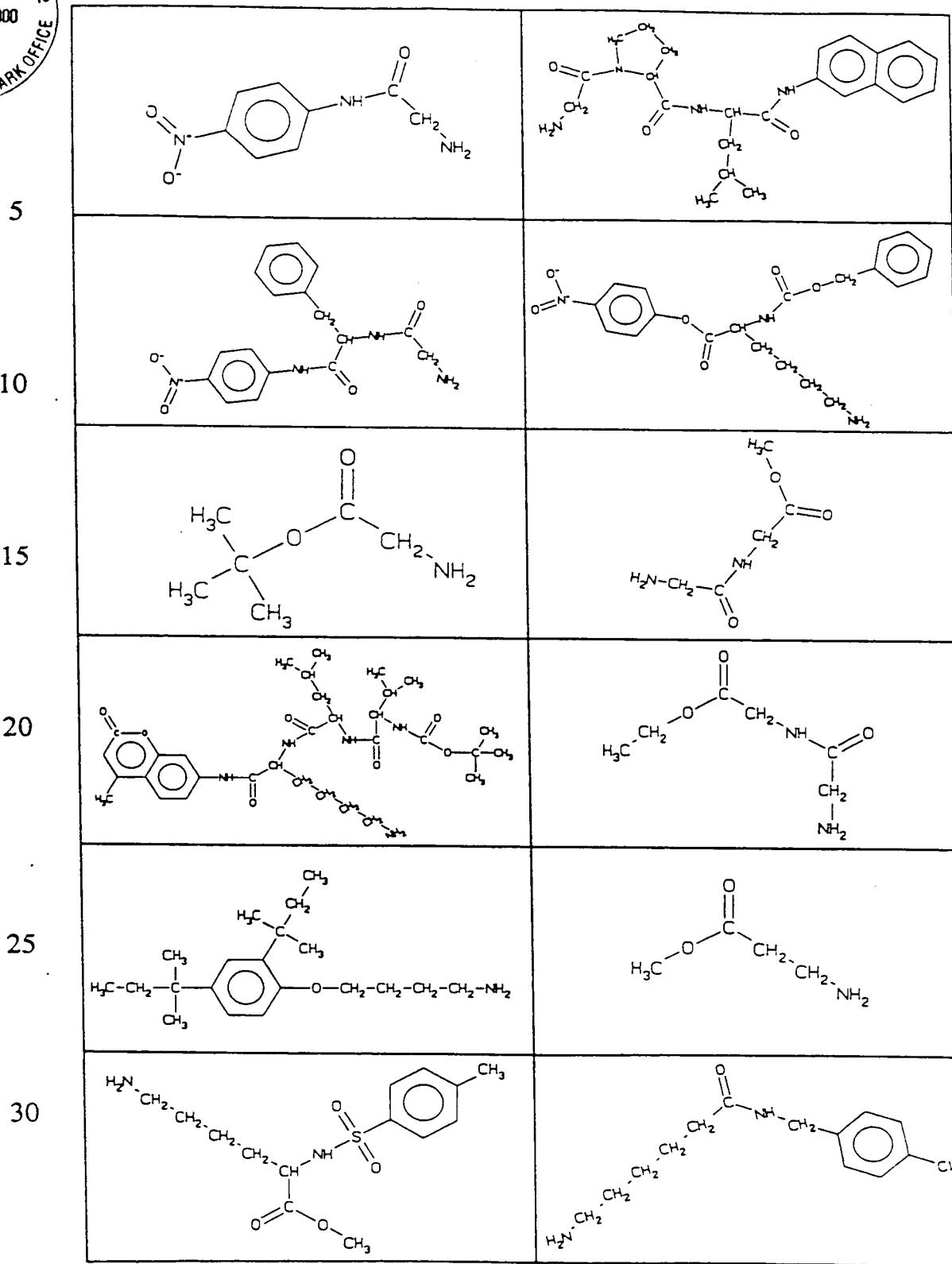


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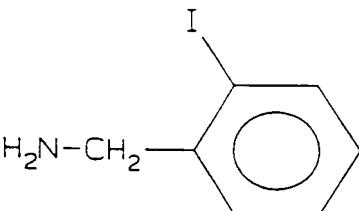
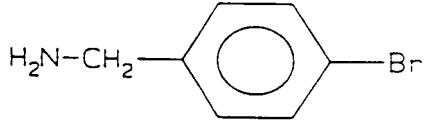
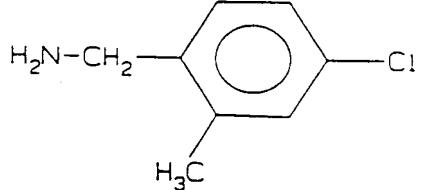
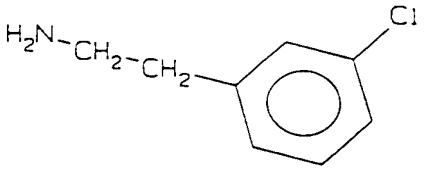
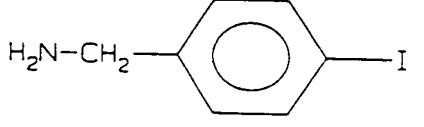
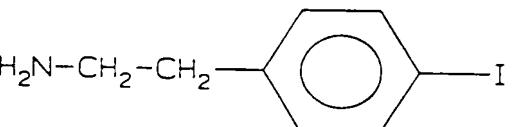
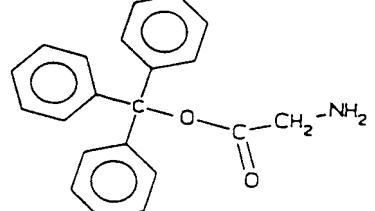
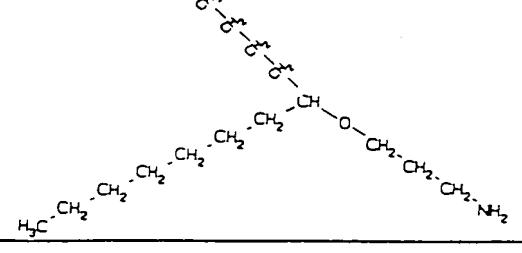
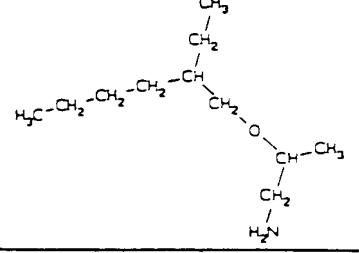
	
	$\text{H}_3\text{C}-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{NH}_2$
	
	
	
	



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 5	$\text{H}_3\text{C}-\text{CH}_2-\text{CH}_2-\text{O}-\text{CH}_2-\text{CH}_2-\text{NH}_2$
 10	$\text{H}_3\text{C}-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{O}-\text{CH}_2-\text{CH}_2-\text{NH}_2$
 15	
 20	
 25	
 30	$\text{H}_3\text{C}-\text{CH}_2-\text{O}-\text{CH}_2-\text{CH}_2-\text{O}-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{NH}_2$

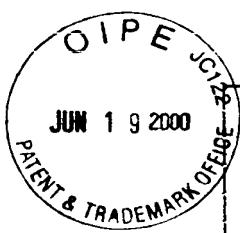
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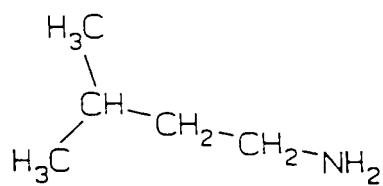
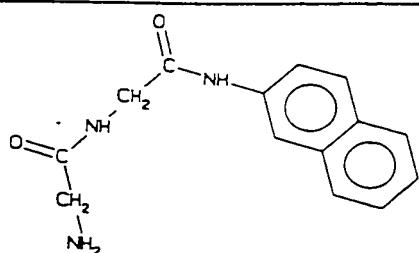
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<p>15</p>	<p>H₃C—O—CH₂—NH₂ F—C₆H₄—Cl</p>
<p>20</p>	<p>H₂N—CH₂—C₆H₄—Cl F</p>
<p>25</p>	<p>H₂N—CH₂—C(F)(F)—C(F)(F)—F</p>
<p>30</p>	<p>H₂N—CH₂—C(F)(F)—C(F)(F)—C(F)(F)—C(F)(F)—C(F)(F)—C(F)(F)—F</p>

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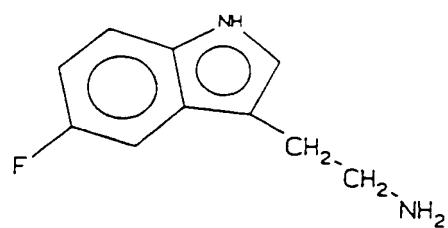
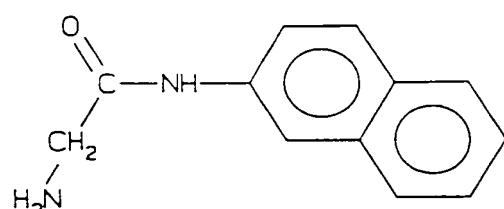
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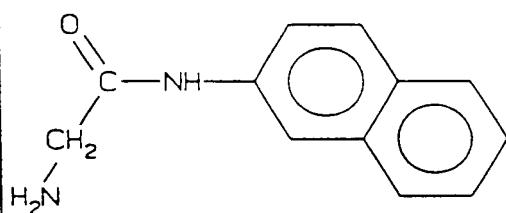
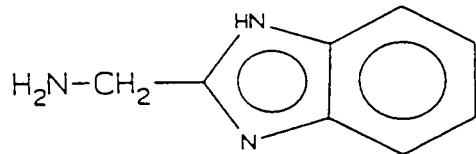
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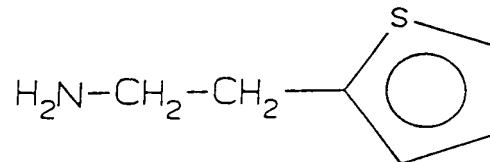
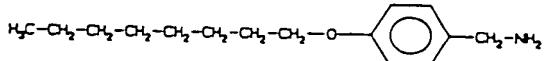
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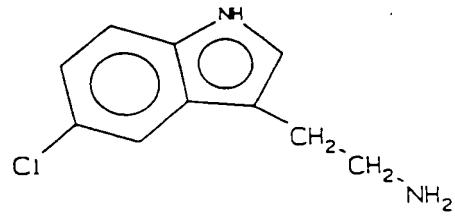
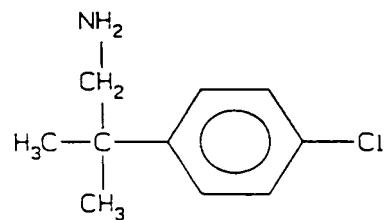
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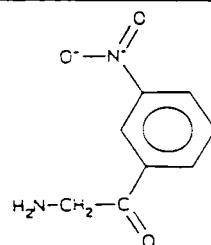
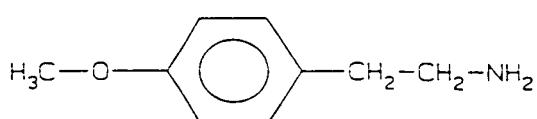
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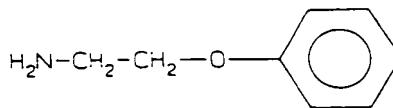
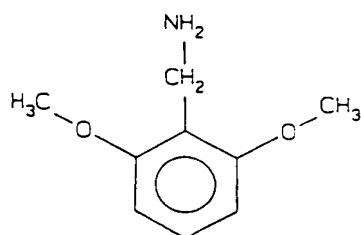
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$\text{H}_3\text{C}-\text{C}(\text{CH}_3)-\text{S}-\text{CH}_2-\text{CH}_2-\text{NH}_2$	
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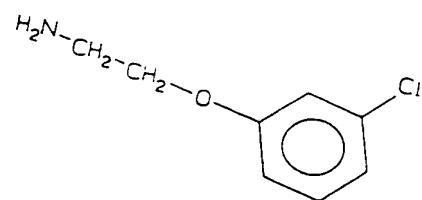
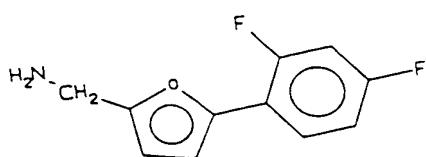
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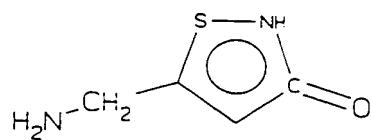
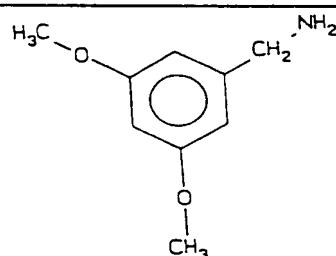
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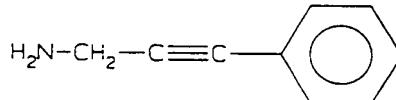
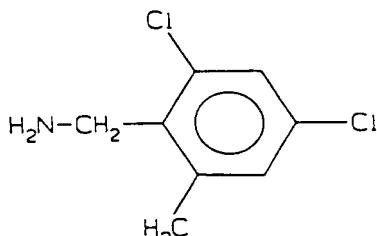
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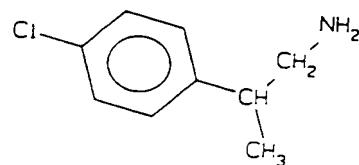
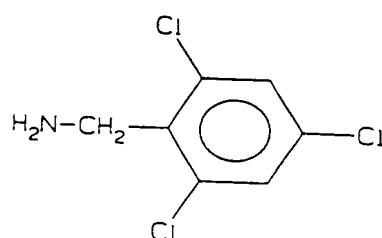
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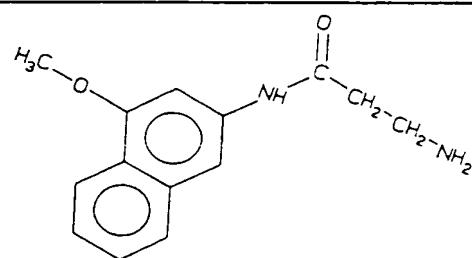
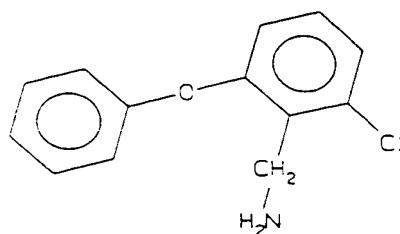
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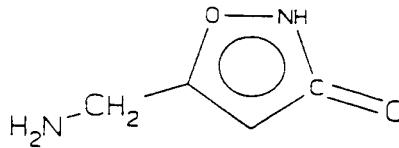
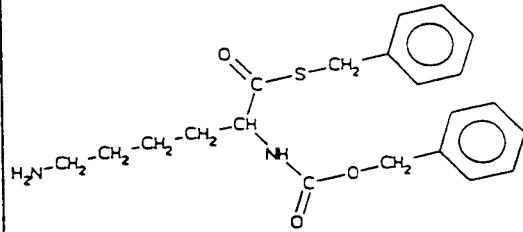
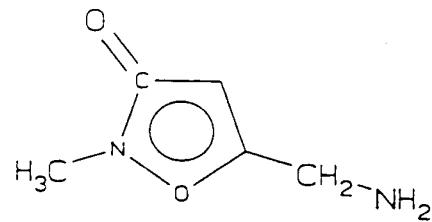
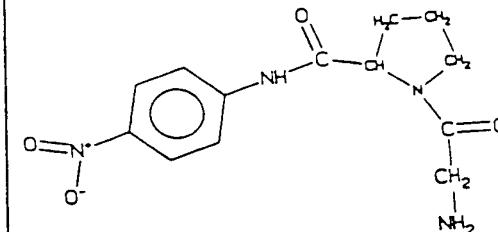
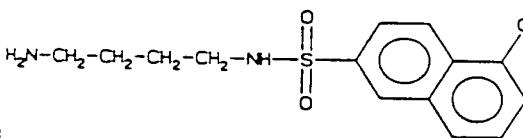
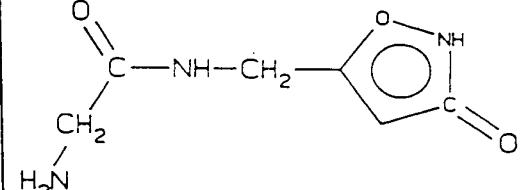
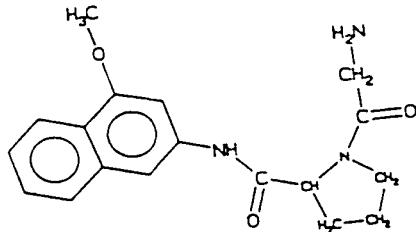
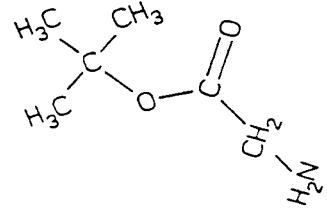
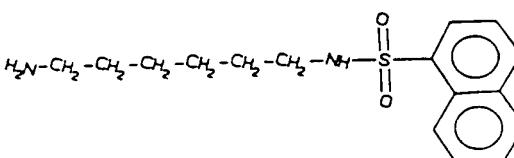
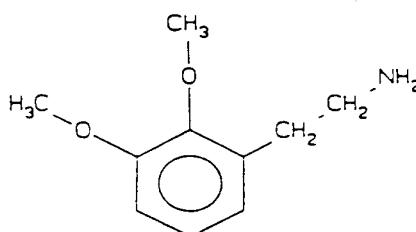
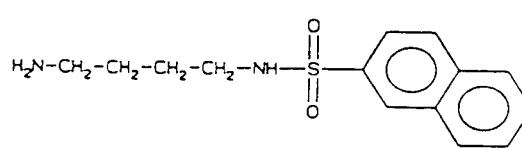
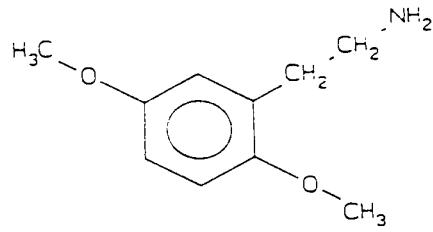
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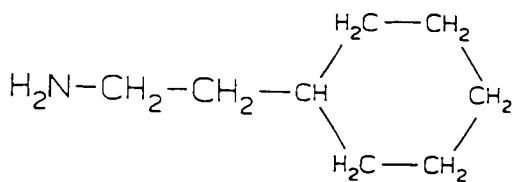
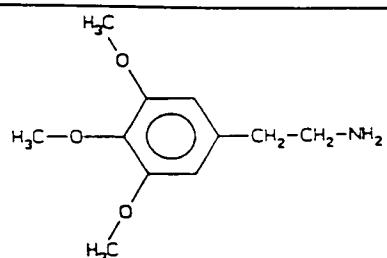


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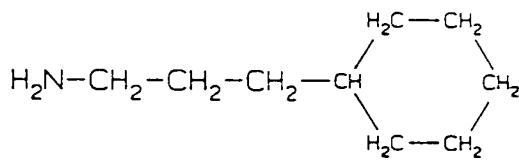
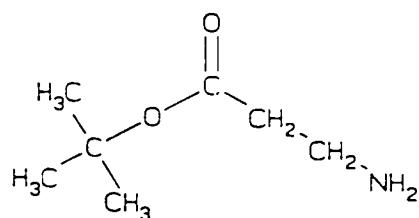
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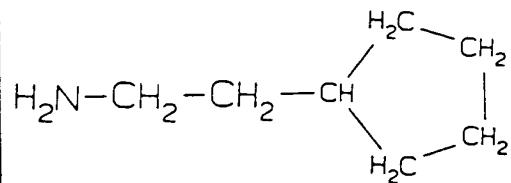
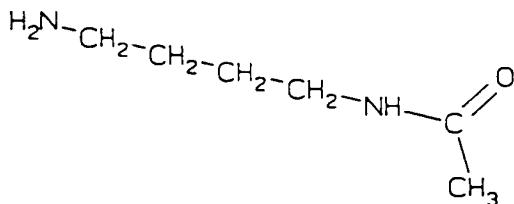
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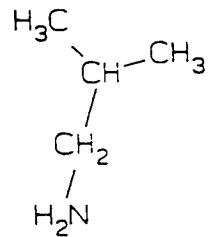
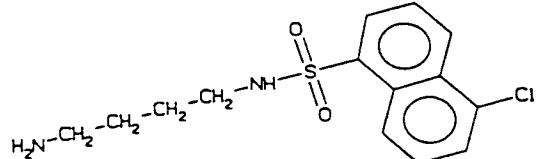
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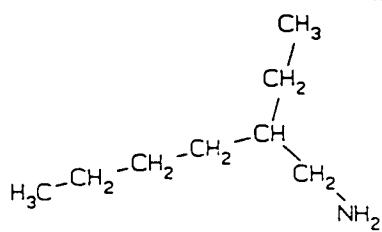
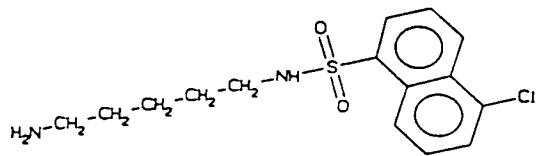
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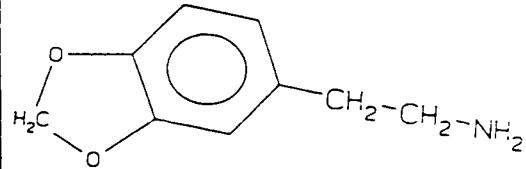
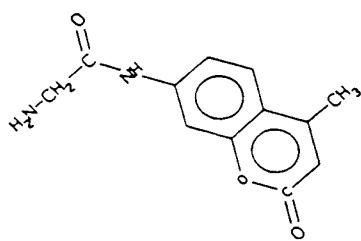
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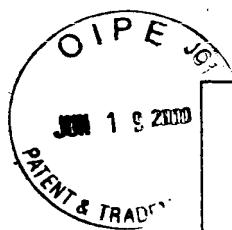
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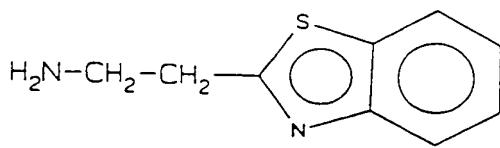
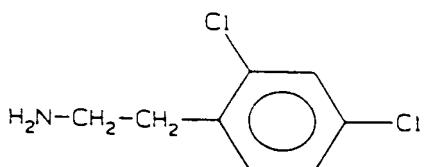
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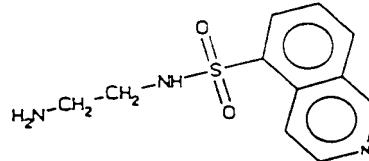
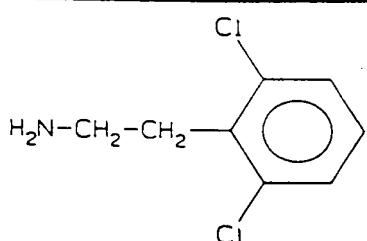
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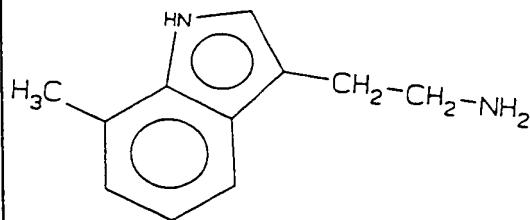
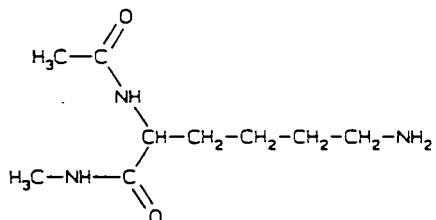
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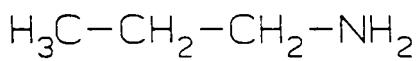
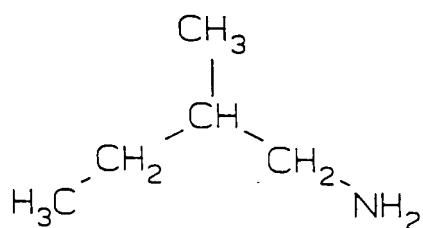
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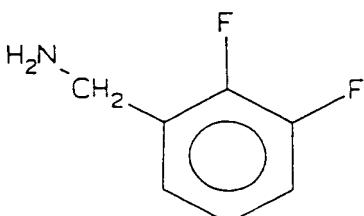
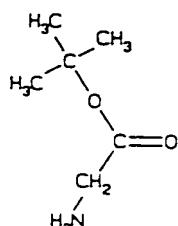
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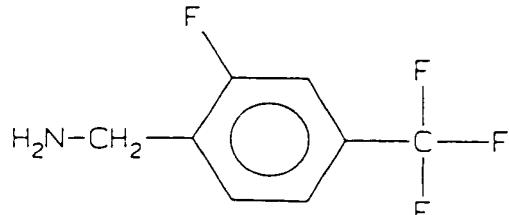
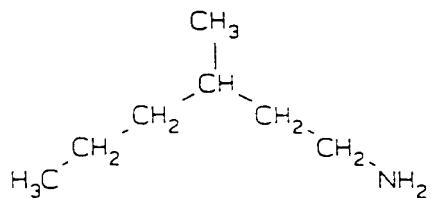
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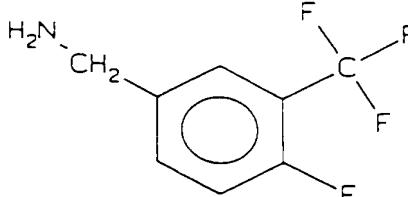
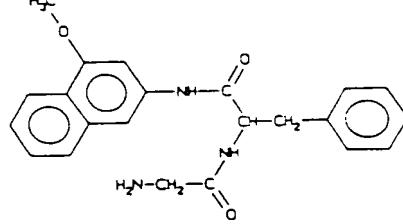
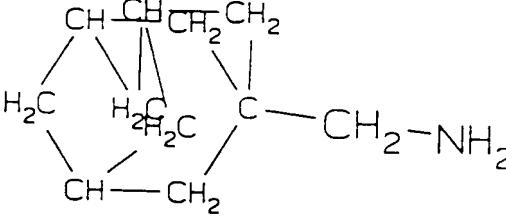
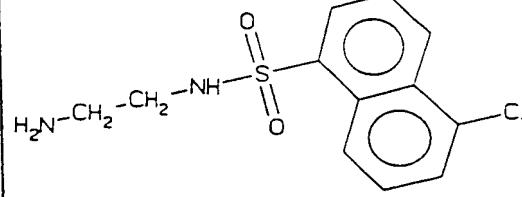
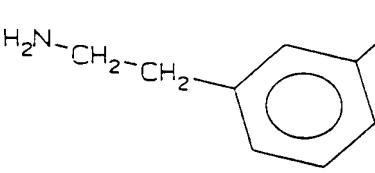
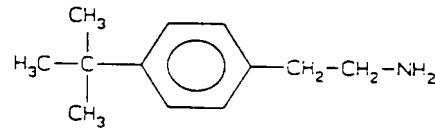
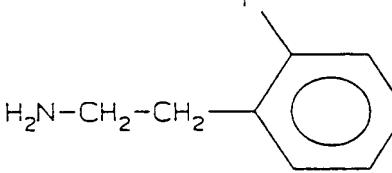
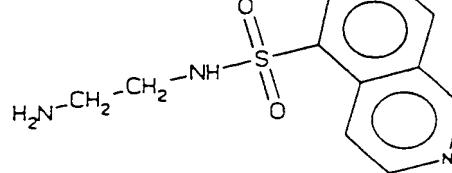
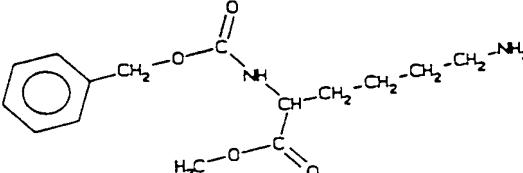
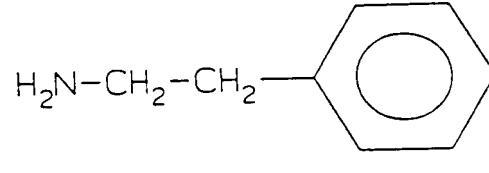
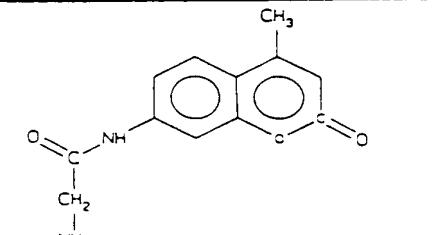
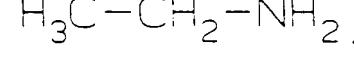


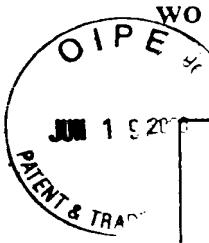
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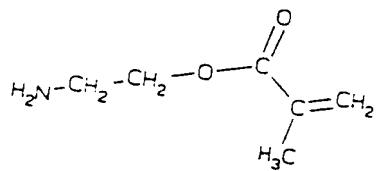
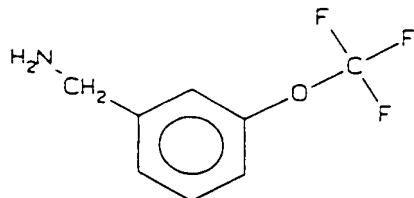
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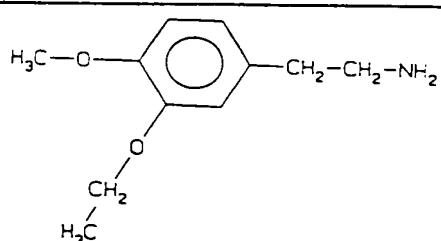
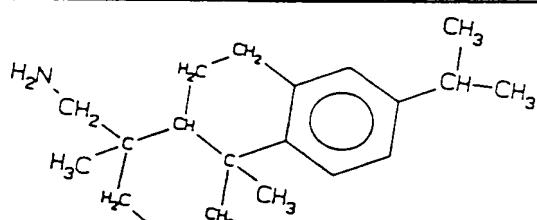
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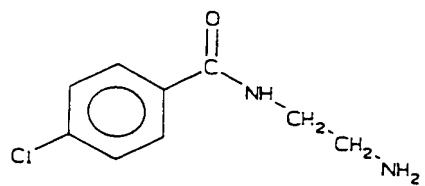
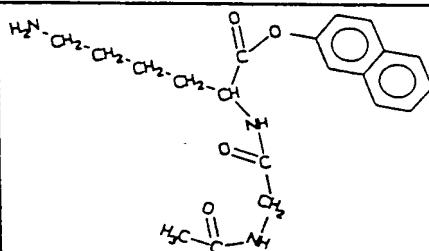
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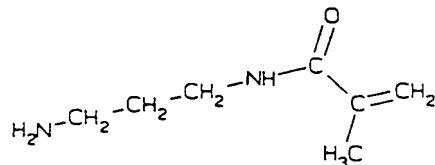
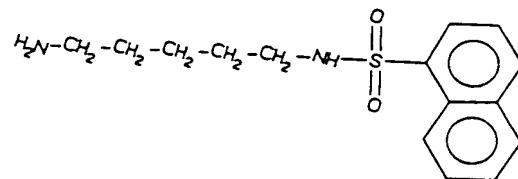
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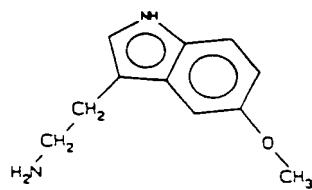
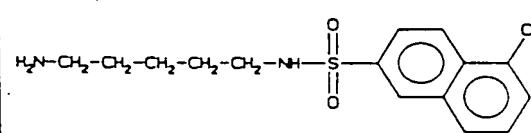
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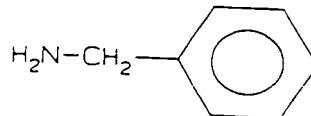
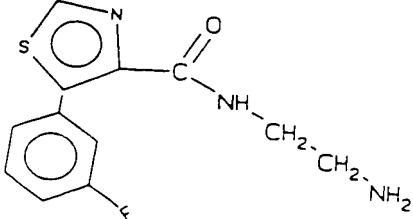
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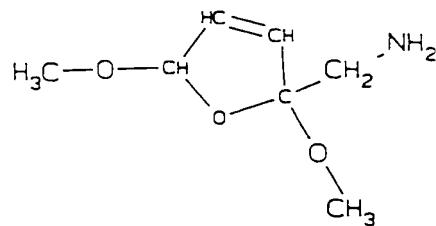
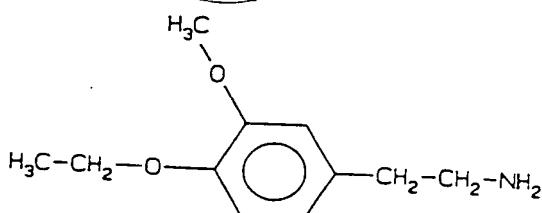
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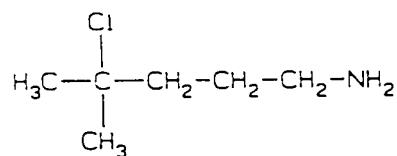
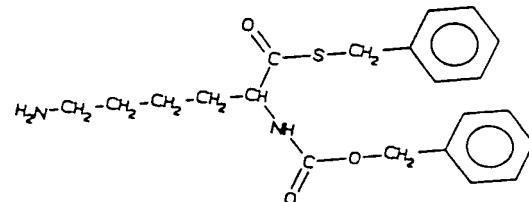
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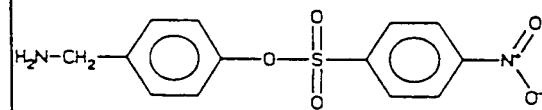
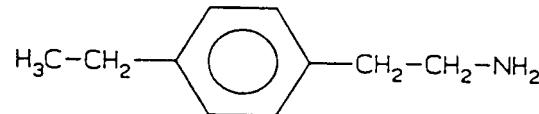
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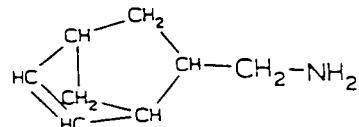
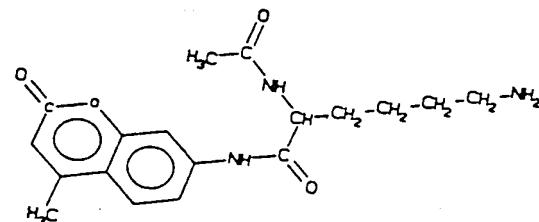
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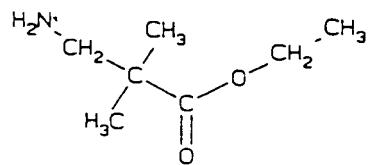
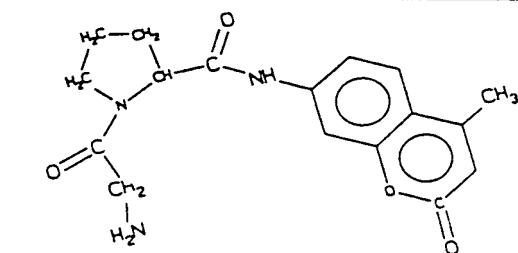
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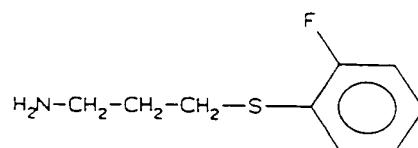
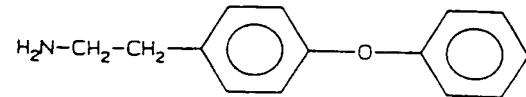
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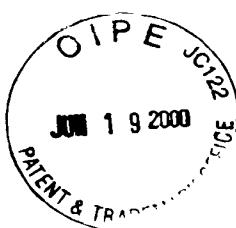
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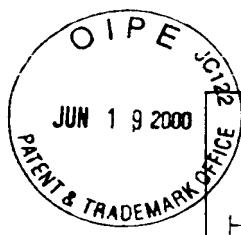
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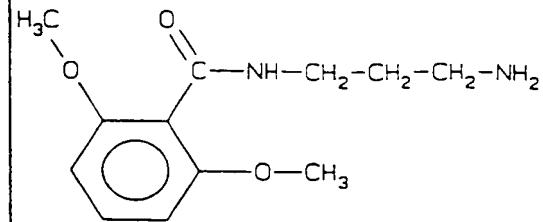
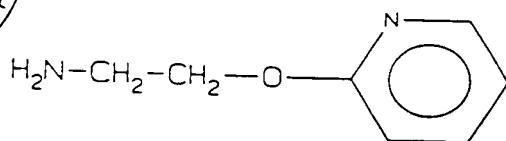
PATENT & TRADEMARK OFFICE
U.S. DEPARTMENT OF COMMERCE
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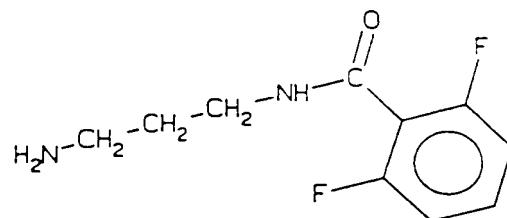
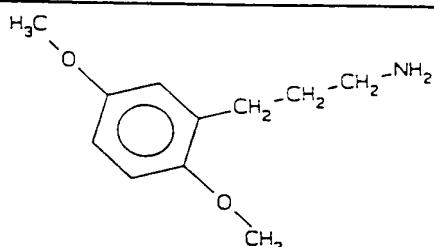
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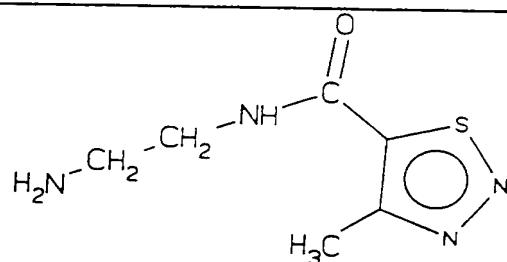
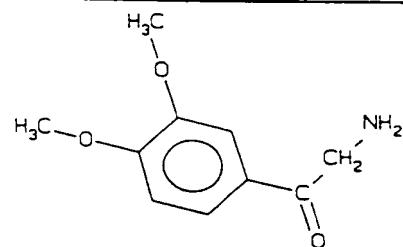
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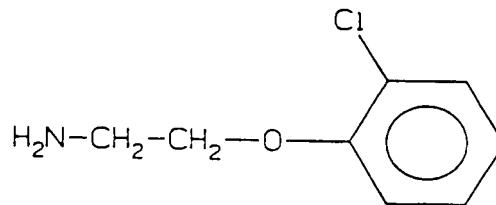
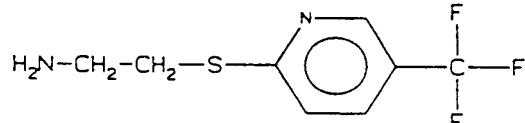
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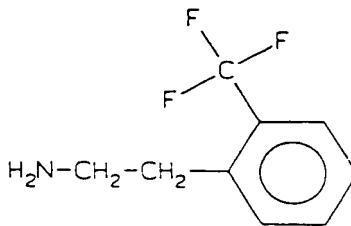
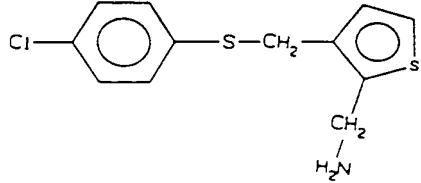
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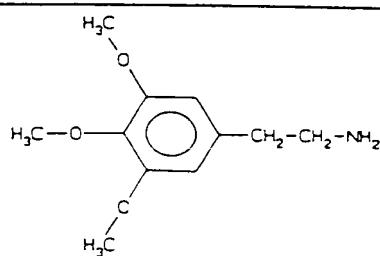
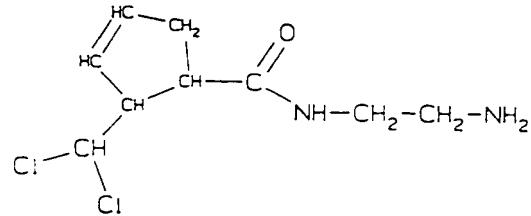
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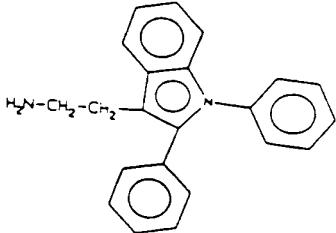
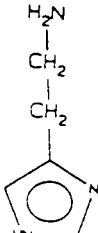
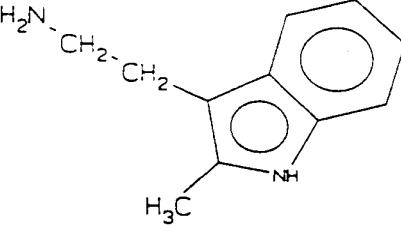
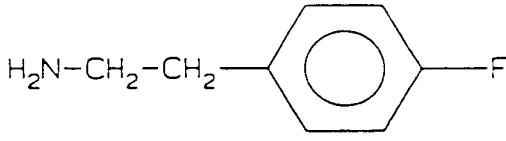
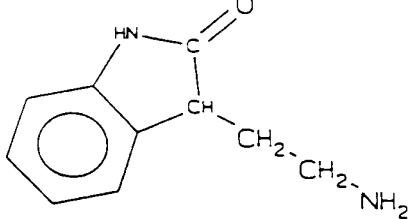
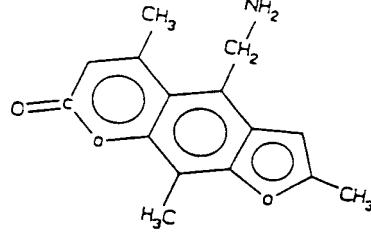
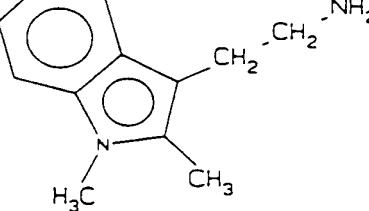
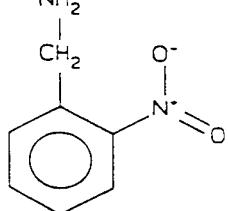
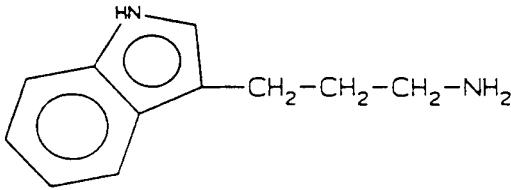
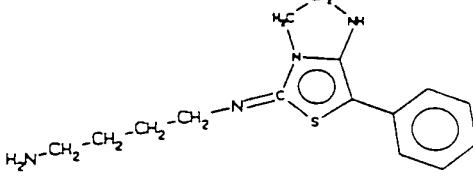
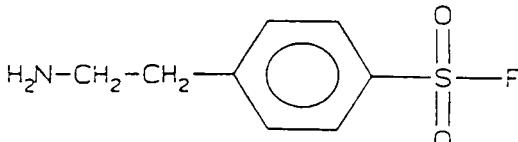
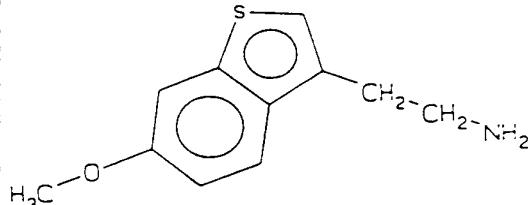


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$\text{H}_3\text{C}-(\text{CH}_2)_{15}-\text{NH}_2$	
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$\text{H}_3\text{C}-\overset{\text{O}}{\underset{\text{C}}{\text{N}}}(\text{CH}_2)_4\text{NH}_2$ $\text{H}_3\text{C}-\overset{\text{O}}{\underset{\text{C}}{\text{N}}}(\text{CH}_2)_4\text{NH}_2$ $\text{O}-\overset{\text{O}}{\underset{\text{C}}{\text{N}}}(\text{CH}_2)_3$	

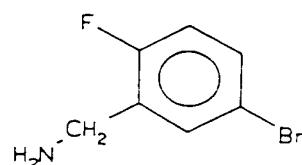
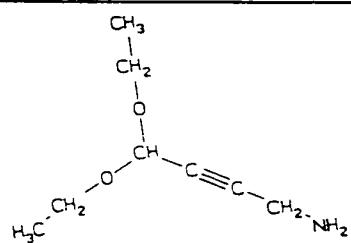
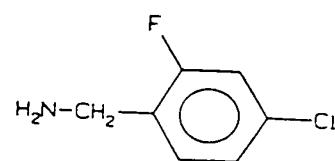
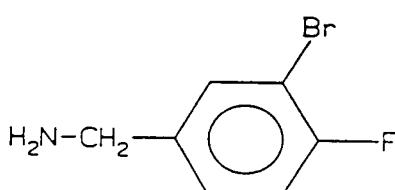
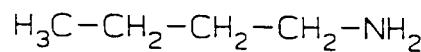
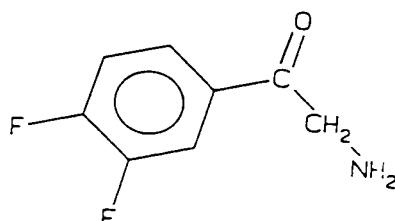
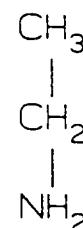
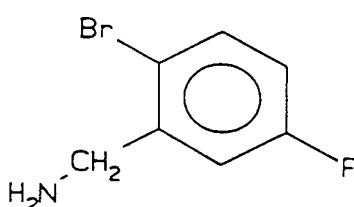
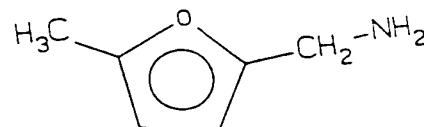
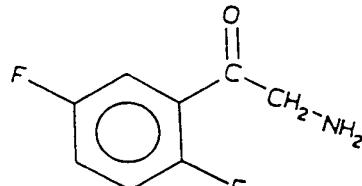
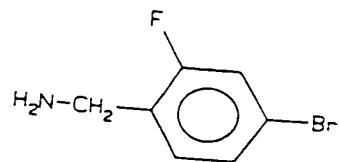
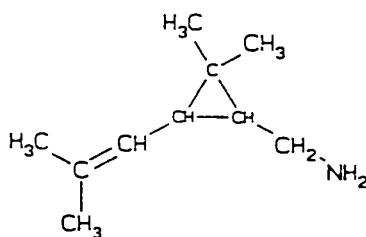
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	$\text{H}_2\text{N}-\text{CH}_2-\text{CH}_2-\text{C}(\text{CH}_3)=\text{C}(\text{CH}_3)\text{CH}_3$
	$\text{H}_2\text{N}-\text{CH}_2-\text{CH}_2-\text{Cl}$
	$\text{H}_3\text{C}-\text{CH}_2-\overset{\text{CH}_3}{\underset{\text{CH}_2}{\text{CH}}}-\overset{\text{CH}_2}{\underset{\text{CH}}{\text{CH}}}-\text{CH}_2-\text{NH}_2$

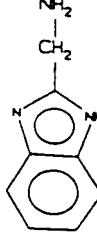
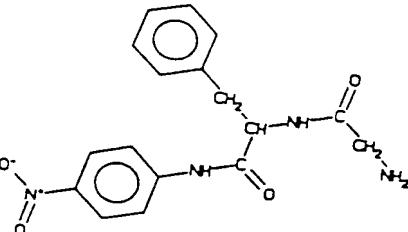
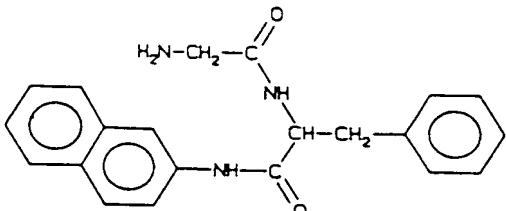
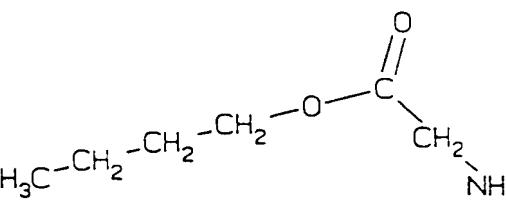
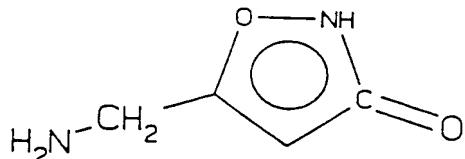
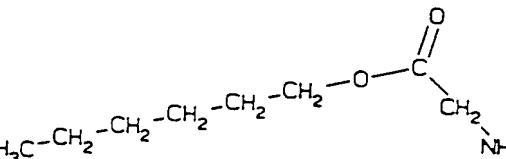
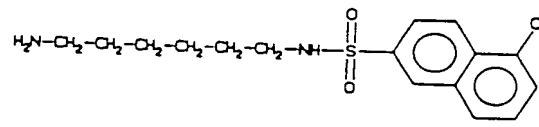
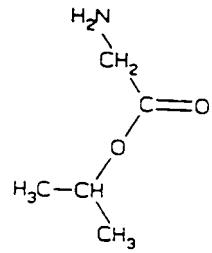
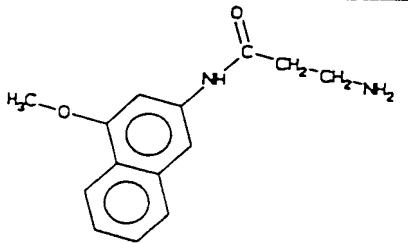
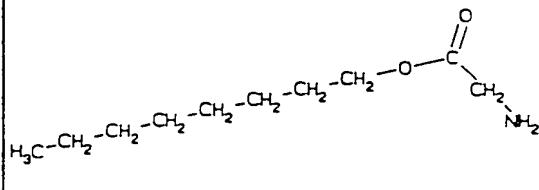
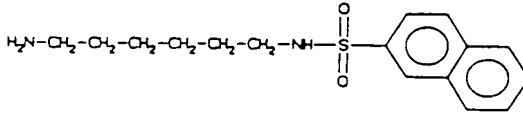
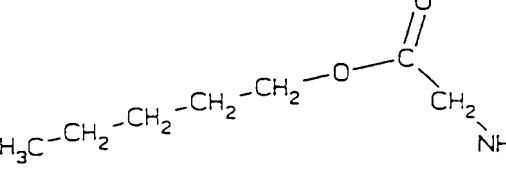
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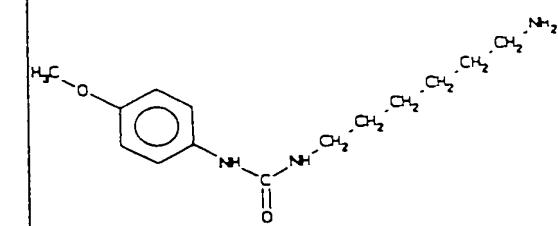
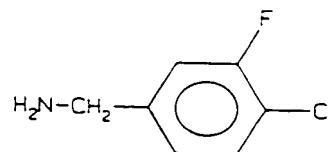


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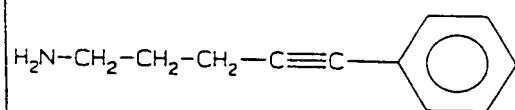
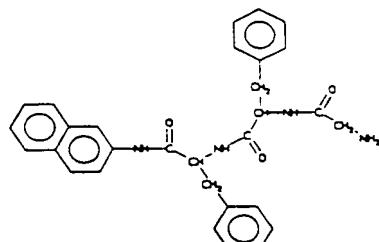
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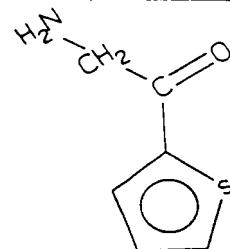
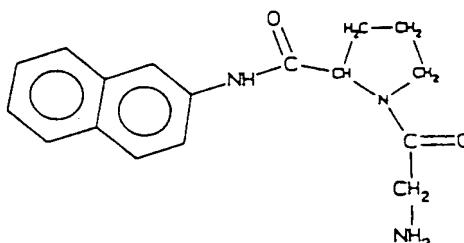
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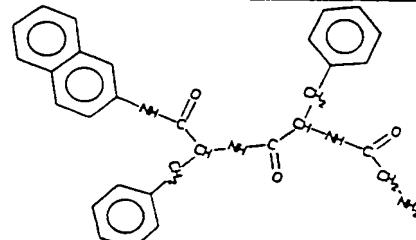
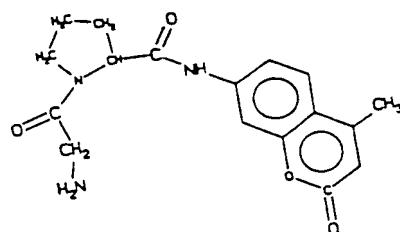
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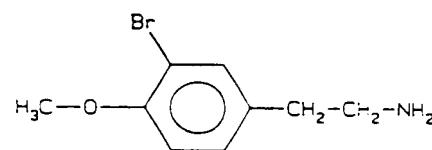
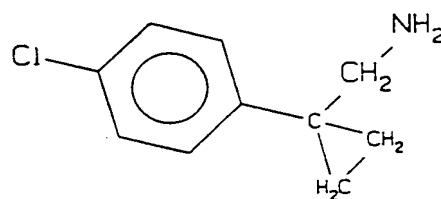
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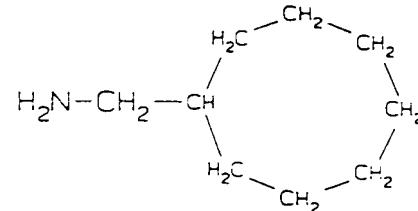
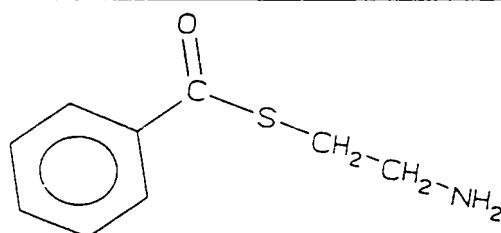
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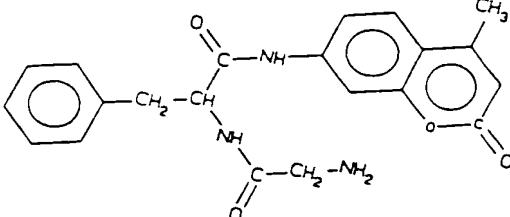
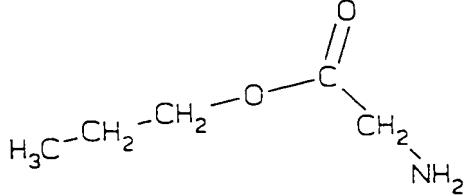
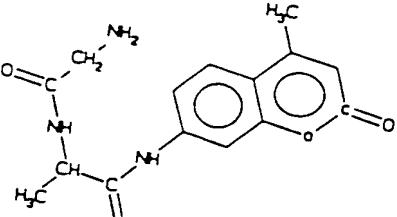
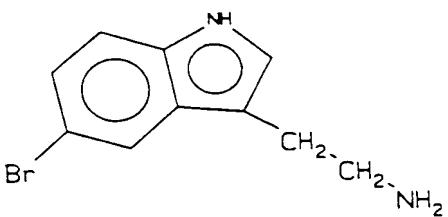
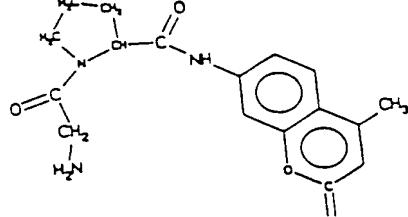
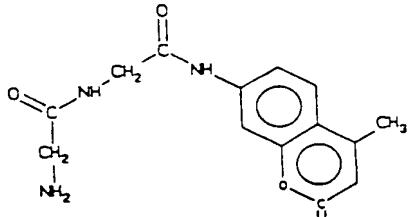
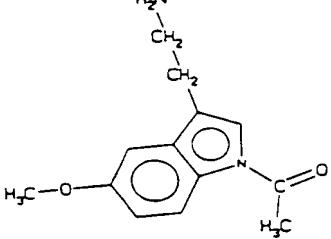
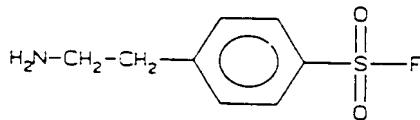
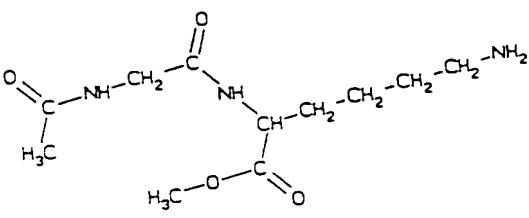
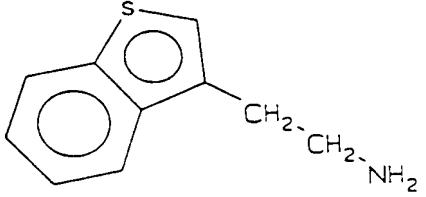
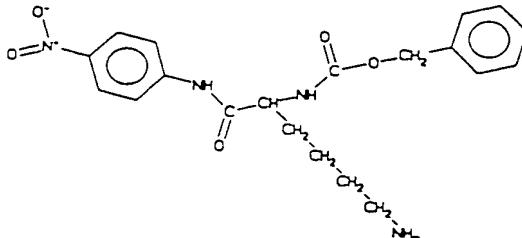
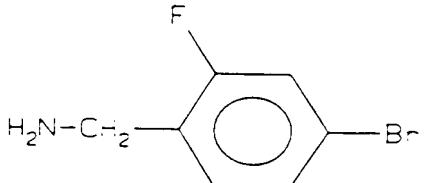
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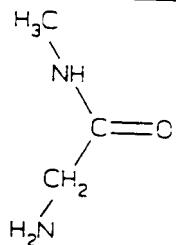
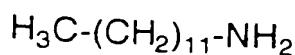
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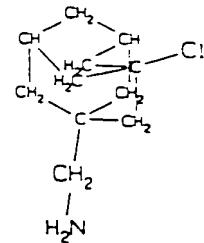
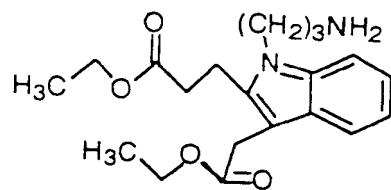
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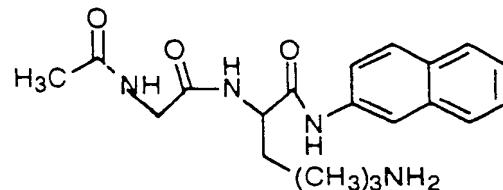
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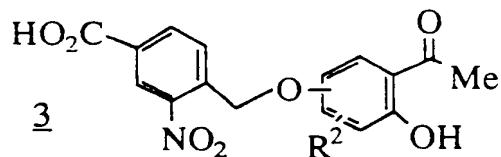
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One embodiment of the invention is the use of the combinatorial library of Formula I in assays to discover biologically active compounds (ligands) of Formula II. Thus, an aspect of the invention is a method of identifying a compound having a desired

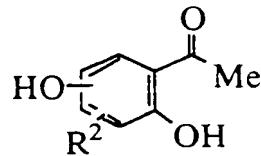
5 characteristic which comprises synthesizing a combinatorial library of Formula I and testing the compounds of Formula I and the ligands of Formula II, either attached to the solid support or detached therefrom, in an assay which identifies compounds having the desired characteristic. A further embodiment of the invention is determining
10 the structure of any compound so identified.

Another embodiment of the invention is a process for preparing a compound of the formula:

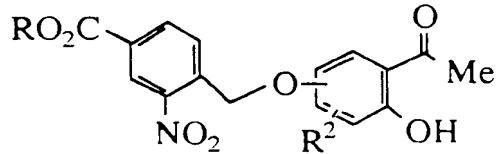


where R² is H or lower alkyl;

15 which comprises a) reacting allyl or methyl 4-(hydroxymethyl)-3-nitrobenzoate with a compound of the formula:



in the presence of triphenylphosphine, toluene, and DEAD and stirring the mixture at room temperature to produce



20

where R is allyl or methyl

and b) when R is allyl reacting said compound with methylene chloride, tetrakistriphenylphosphine palladium(0), and pyrrolidine and stirring



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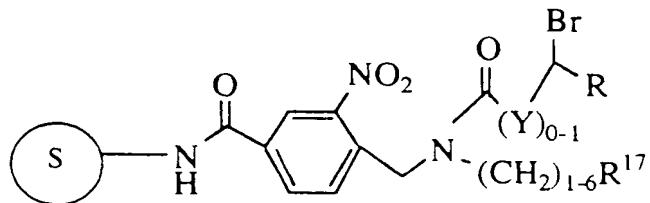
the mixture at 0°C, or when R is methyl reacting said compound with dilute NaOH and THF and stirring the mixture at 0°C.

For this reaction, R=allyl is preferable to the t-butyl or methyl esters since the milder conditions would not induce aldol type condensation of the acetophenone portion of the molecule.

Another embodiment of the invention is a method for identifying compounds that are inhibitors of carbonic anhydrase which comprises preparing a mixture of 20-300 pmol test compound and aqueous solutions (total volume: 25-100, preferably about 50, μL) of 10 0.03-0.12, preferably about 0.06, μM carbonic anhydrase and 0.04-0.16, preferably about 0.08, μM dansylamide, exposing said mixture to U.V. (preferably 274 nm) light, and determining the amount of emitted U.V. (preferably 454 nm) light.

Another embodiment of the invention is a method for 15 identifying compounds that are enzyme inhibitors which is a lawn assay which comprises contacting a colloidal matrix containing enzyme, which matrix has embedded therein a mono-layer of solid supports with attached ligands, with a layer of fluorogenic substrate-containing material, eluting said ligands by exposure to U.V. light, and detecting 20 zones of inhibition in the colloidal matrix produced thereby. A preferred such lawn assay comprises contacting an agarose matrix containing bovine carbonic anhydrase with a fluorescein diacetate-containing layer of agarose.

Another embodiment of the invention is a compound of the 25 formula:



14

wherein:



(S) is a solid support;
 R is H or alkyl;
 R¹⁶ is lower alkyl, substituted lower alkyl, aryl, or substituted aryl;
 5 R¹⁷ is H; alkyl substituted by 1-3 alkoxy, S-loweralkyl, sulfamoyl, halo, alkylsulphonamido, or arylsulphonamido; alkenyl; alkynyl; aryl; substituted aryl; heteroaryl; substituted heteroaryl; heterocycloalkyl; -CH₂NR¹⁶C(O)R¹⁶; -C(O)NR¹⁶R¹⁶; -CH₂OC(O)R¹⁶; or -CH₂SC(O)R¹⁶; and
 10 Y is aryl or heteroaryl.

Compounds of formula 14 are useful as intermediates in the construction of combinatorial libraries and are especially useful in automated or batch mode syntheses thereof.

15 Definitions

The following abbreviations have the indicated meaning:

Boc	=	t-butyloxycarbonyl
c-	=	cyclo
DEAD	=	diethylazodicarboxylate
20 DBU	=	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	=	dichloromethane = methylene chloride
DIC	=	diisopropylcarbodiimide
DMAP	=	4-N,N-dimethylaminopyridine
DMF	=	N,N-dimethylformamide
25 DMSO	=	dimethyl sulfoxide
DVB	=	1,4-divinylbenzene
EDT	=	1,2-ethanedithiol
equiv.	=	equivalent
Et	=	ethyl
30 FACS	=	fluorescence activated cell sorting
Fmoc	=	9-fluorenylmethoxycarbonyl
GC	=	gas chromatography
HOBt	=	N-hydroxybenzotriazole
hr	=	hour, hours



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	im	=	imidazole
	in	=	indole
	m-	=	meta
	Me	=	methyl
10	Mtr	=	4-methoxy-2,3,6-trimethylbenzenesulfonyl
	n-	=	normal
	Naph	=	naphthyl
	p-	=	para
	PEG	=	Polyethylene glycol
15	Ph	=	phenyl
	Phe	=	phenylene
	Pmc	=	2,2,5,7,8-pentamethylchroman-6-sulfamoyl
	Py	=	pyridyl
	r.t.	=	room temperature
20	sat'd	=	saturated
	s-	=	secondary
	t-	=	tertiary
	t-Boc	=	t-butyloxycarbonyl
	TFA	=	trifluoroacetic acid
	THF	=	tetrahydrofuran

"Alkyl" is intended to include linear, branched, or cyclic structures and combinations thereof of from 1 to 20 carbon atoms.

"Lower alkyl" includes alkyl groups of from 1 to 8 carbon atoms.

Examples of lower alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, s- and t-butyl, pentyl, hexyl, octyl, c-propyl, c-butyl and the like. "Lower cycloalkyl" includes cycloalkyl groups of from 3 to 8 carbon atoms. Examples of lower cycloalkyl groups include c-propyl, c-butyl, c-pentyl, 2-methylcyclopropyl, cyclopropylmethyl, and the like.

30 "Alkenyl" is C₂-C₆ alkenyl of a linear, branched, or cyclic (C₅-C₆) configuration and combinations thereof. Examples of alkenyl groups include allyl, isopropenyl, pentenyl, hexenyl, c-hexenyl, 1-propenyl, 2-but enyl, 2-methyl-2-but enyl, and the like.

35 "Alkynyl" is C₂-C₆ alkynyl of a linear, branched, or cyclic (C₅-C₆) configuration and combinations thereof. Examples of alkynyl groups include ethynyl, propargyl, 3-methyl-1-pentynyl, 2-heptynyl



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isopropynyl, pentynyl, hexynyl, c-hexynyl, 1-propynyl, 2-butynyl, 2-methyl-2-butynyl, and the like.

"Alkoxy" means alkoxy groups of from 1 to 6 carbon atoms of a straight, branched, or cyclic configuration. Examples of 5 alkoxy groups include methoxy, ethoxy, propoxy, isopropoxy, cyclopropoxy, cyclohexyloxy, and the like.

"Substituted loweralkyl" means lower alkyl substituted with 1-3 alkoxy, carboalkoxy, carboxamido, di-loweralkylamino, aryl, substituted aryl, or heteroaryl.

10 "Aryl" means phenyl or naphthyl.

"Substituted aryl" means aryl substituted with 1-3 halo, loweralkyl, alkoxy, aryl, S-loweralkyl, alkylsulphonamido, arylsulphonamido, or sulfamoyl.

15 "Heteroaryl" means a 5 or 6 membered aromatic ring containing 1-3 hetero atoms selected from O, N, and S.

"Substituted heteroaryl" means heteroaryl substituted with 1-3 halo, loweralkyl, alkoxy, aryl, S-loweralkyl, alkylsulphonamido, arylsulphonamido, or sulfamoyl.

20 "Heterocycloalky" means lower cycloalkyl containing 1-3 hetero atoms selected from O, N, and S.

Halogen includes F, Cl, Br, and I.

25 L and L' are depicted in Table 1, which also shows cleavage reagents. In designing a synthetic scheme, L and L' are chosen such that they are orthogonally reactive; i.e., they must allow for removal of either T or II (where T = T'-OH) without removal of the other since simultaneous cleavage of both T and II from the solid support is disadvantageous. In the structures as shown, the left-hand bond is the point of attachment to the solid support and the right-hand bond is the point of attachment to either T or II.



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TABLE 1
LINKER GROUPS

	Linker Group	Cleavage Reagent
5	1.	$h\nu$
	2.	$h\nu$
10	3.	$\text{Ce}(\text{NH}_4)_2(\text{NO}_3)_6$
15	4.	$\text{Ce}(\text{NH}_4)_2(\text{NO}_3)_6$
	5. $-\text{CH}=\text{CH}(\text{CH}_2)_2-$	$\text{O}_3, \text{OsO}_4/\text{IO}_4^-$, or KMnO_4
	6. $-\text{CH}=\text{CHCH}_2-$	$\text{O}_3, \text{CsO}_4/\text{IO}_4^-$, or KMnO_4
	7. $-\text{CH}_2\text{CH}=\text{CH}-$	$\text{O}_3, \text{OsO}_4/\text{IO}_4^-$, or KMnO_4
20	8.	1) O_2 or Br_2, MeOH 2) H_3O^+
	9. $-\text{CH}=\text{CHCH}_2\text{O}-$	$(\text{Ph}_3\text{P})_3\text{RhCl}(\text{H})$
	10.	$\text{Li}, \text{Mg}, \text{or BuLi}$
25	11. $-\text{S}-\text{CH}_2\text{O}-$	Hg^{+2}
	12.	Zn or Mg
	13.	Oxidation, e.g., $\text{Pb}(\text{OAc})_4$ or H_5IO_6

30 R = H or lower alkyl

X = electron withdrawing group such as Br, Cl, and I.



The tags of this invention, T, are chemical entities which possess several properties: they must be detachable from the solid supports, preferably by photolysis or oxidation; they must be individually differentiable, and preferably separable; they must be 5 stable under the synthetic conditions; they must be capable of being detected at very low concentrations, e.g., 10^{-18} to 10^{-9} mole; they should be identifiable with readily-available equipment which does not require sophisticated technical capabilities to operate; and they should be relatively economical. The tags may be structurally related or 10 unrelated, e.g., a homologous series, repetitive functional groups, related members of the Periodic Chart, different isotopes, combinations thereof, and the like. At the end of the combinatorial synthesis, to each solid support, there will usually be attached at least 0.01 femtomol, usually 0.001-50 pmol, of each tag. The tags may be aliphatic, 15 alicyclic, aromatic, heterocyclic, or combinations thereof. Distinguishing features may be the number of repetitive units, such as methylene groups in an alkyl moiety; alkyleneoxy groups in a polyalkyleneoxy moiety; halo groups in a polyhalo compound; α - and/or β -substituted ethylene groups where the substituents may be 20 alkyl groups, oxy, carboxy, amino, halo, or the like; isotopes; etc.

The materials upon which the combinatorial syntheses of the invention are performed are referred to as solid supports, beads, and resins. These terms are intended to include:

- a) beads, pellets, disks, fibers, gels, or particles such as 25 cellulose beads, controlled pore-glass beads, silica gels, polystyrene beads optionally cross-linked with divinylbenzene and optionally grafted with polyethylene glycol and optionally functionalized with amino, hydroxy, carboxy, or halo groups, grafted co-poly beads, poly-acrylamide beads, latex beads, dimethylacrylamide beads optionally 30 cross-linked with N,N'-bis-acryloyl ethylene diamine, glass particles coated with hydrophobic polymer, etc., i.e., material having a rigid or semi-rigid surface; and
- b) soluble supports such as low molecular weight non-cross-linked polystyrene.



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It is intended that the definitions of any substituent or symbol (e.g., R³) in a particular molecule be independent of its definitions elsewhere in the molecule. Thus, NR³R³ represents NH₂, NHCH₃, N(CH₃)₂, etc.

5 Optical Isomers - Diastereomers - Geometric Isomers - Tautomers

Some of the compounds described herein contain one or more asymmetric centers and may thus give rise to enantiomers, diastereomers, and other stereoisomeric forms which may be defined in terms of absolute stereochemistry as (R) or (S). The present invention
10 is meant to comprehend all such possible diastereomers as well as their racemic and optically pure forms and mixtures thereof. Optically active (R) and (S) forms may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques. When the compounds described herein contain olefinic double bonds or other
15 centers of geometric asymmetry, and unless specified otherwise, it is intended to include both E and Z geometric isomers. Likewise, all tautomeric forms are intended to be included.

Salts

The pharmaceutical compositions of the present invention
20 comprise a compound of Formula II as an active ingredient or a pharmaceutically acceptable salt thereof, and may also contain a pharmaceutically acceptable carrier and, optionally, other therapeutic ingredients. The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic acids or bases
25 including organic and inorganic acids or bases.

When a compound of the present invention is acidic, salts may be prepared from pharmaceutically acceptable non-toxic bases. Salts derived from all stable forms of inorganic bases include aluminum, ammonium, calcium, copper, iron, lithium, magnesium,
30 manganese, potassium, sodium, zinc, etc. Particularly preferred are the ammonium, calcium, magnesium, potassium, and sodium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion-exchange resins such as arginine, betaine, caffeine,



choline, N,N'-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, isopropylamine, lysine, methylglucosamine, 5 morpholine, piperazine, piperidine, polyamine resins, procaine, purine, theobromine, triethylamine, trimethylamine, tripropylamine, etc.

When a compound of the present invention is basic, salts may be prepared from pharmaceutically acceptable non-toxic acids. Such acids include acetic, benzenesulfonic, benzoic, camphorsulfonic, 10 citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic, etc. Particularly preferred are citric, hydrobromic, maleic, phosphoric, sulfuric, and tartaric acids.

15 In the discussion of methods of treatment herein, reference to the compounds of Formula II is meant to also include the pharmaceutically acceptable salts thereof.

Utilities

20 The ability of the compounds of Formula II to interact with α adrenergic receptors indicates that the compounds are useful to treat, prevent, or ameliorate hypertension and benign prostate hypertrophy in mammals, especially in humans.

25 The ability of the compounds of Formula II to interact with dopamine receptors indicates that the compounds are useful to treat, prevent, or ameliorate Alzheimer's disease and depression in humans.

30 The ability of the compounds of Formula II to interact with σ -opiate receptors indicates that the compounds are useful to treat, prevent, or ameliorate schizophrenia in mammals, especially in humans.

35 The ability of the compounds of Formula II to interact with K^+ channels indicates that the compounds are useful to treat, prevent, or ameliorate hypertension, asthma, and pulmonary insufficiency in mammals, especially in humans.

The ability of certain compounds of Formula II to inhibit carbonic anhydrase isozymes makes them useful for preventing or reversing the symptoms induced by these enzymes in a mammal. This



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enzyme inhibition indicates that the compounds are useful to treat, prevent, or ameliorate ocular diseases, particularly glaucoma in mammals, especially in humans.

Dose Ranges

5 The magnitude of the prophylactic or therapeutic dose of the compounds of Formula II will vary with the nature and severity of the condition to be treated and with the particular compound of Formula II and its route of administration. In general, the daily dose range for anti-enzymic use lies in the range of 20 to 0.001 mg/kg body weight of a mammal, preferably 10 to 0.01 mg/kg, and most preferably 1.0 to 0.1 mg/kg, in single or divided doses. In some cases, it may be necessary to use doses outside these ranges.

10 When a composition for intravenous administration is employed, a suitable daily dosage range is from about 10 to 0.0005 mg (preferably 5 to 0.01 mg) compound of Formula II per kg body weight.

15 When a composition for oral administration is employed, a suitable daily dosage range is from about 20 to 0.001 mg (preferably 10 to 0.01 mg) compound of Formula II per kg body weight.

20 When a composition for ophthalmic administration is employed, a suitable daily dosage range is from about 10-0.01% (preferably 5.0-0.5% compound of Formula II, typically prepared as a 2.0-0.1% by weight solution or suspension of a compound of Formula II in an acceptable ophthalmic formulation.

25 The compounds of Formula II may also be used in combination with other pharmaceutically active ingredients. For example, a typical ocular formulation may comprise the compound alone or in combination with a β -adrenergic blocking agent such as timolol maleate or a parasympathomimetic agent such as pilocarpine. When used in combination, the two active ingredients are present in approximately equal parts.

30

35

Pharmaceutical Compositions

Any suitable route of administration may be employed for providing a mammal, especially a human, with an effective dosage of a compound of Formula II. For example, oral, rectal, topical, parenteral, ocular, pulmonary, nasal, etc. routes may be employed. Dosage forms



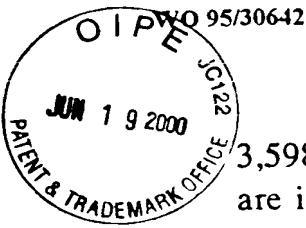
include tablets, troches, dispersions, suspensions, solutions, capsules, creams, ointments, aerosols, and the like.

5 The pharmaceutical compositions of the present invention comprise a compound of Formula II, or a pharmaceutically acceptable salt thereof, as an active ingredient, and may also contain a pharmaceutically acceptable carrier and, optionally, other therapeutically active ingredients.

10 The compositions include compositions suitable for oral, rectal, topical (including transdermal devices, aerosols, creams, ointments, lotions, and dusting powders), parenteral (including subcutaneous, intramuscular, and intravenous), ocular (ophthalmic), pulmonary (nasal or buccal inhalation), or nasal administration; although the most suitable route in any given case will depend largely 15 on the nature and severity of the condition being treated and on the nature of the active ingredient. They may be conveniently presented in unit dosage form and prepared by any of the methods well known in the art of pharmacy.

20 A compound of Formula II may be combined as the active ingredient in intimate admixture with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The carrier may take a wide variety of forms depending on the nature of the preparation desired for administration, i.e., oral, parenteral, etc. In preparing oral dosage forms, any of the usual pharmaceutical media 25 may be used, such as water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents, and the like in the case of oral liquid preparations (e.g., suspensions, elixirs, and solutions); or carriers such as starches, sugars, microcrystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents, etc. in the case of oral solid preparations such as powders, capsules, and tablets. Solid oral 30 preparations are preferred over liquid oral preparations. Because of their ease of administration, tablets and capsules are the preferred oral dosage unit form. If desired, capsules may be coated by standard aqueous or non-aqueous techniques.

35 In addition to the dosage forms described above, the compounds of Formula II may be administered by controlled release means and devices such as those described in U.S.P. Nos. 3,536,809;



3,598,123; 3,630,200; 3,845,770; 3,916,899; and 4,008,719, which are incorporated herein by reference.

Pharmaceutical compositions of the present invention suitable for oral administration may be prepared as discrete units such as capsules, cachets, or tablets each containing a predetermined amount of the active ingredient in powder or granular form or as a solution or suspension in an aqueous or nonaqueous liquid or in an oil-in-water or water-in-oil emulsion. Such compositions may be prepared by any of the methods known in the art of pharmacy. In general, the compositions are prepared by uniformly and intimately admixing the active ingredient with liquid carriers, finely divided solid carriers, or both and then, if necessary, shaping the product into the desired form. For example, a tablet may be prepared by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as powder or granule optionally mixed with a binder, lubricant, inert diluent, or surface active or dispersing agent. Molded tablets may be made by molding in a suitable machine, a mixture of the powdered compound moistened with an inert liquid diluent. Ophthalmic inserts are made from compression molded films which are prepared on a Carver Press by subjecting the powdered mixture of active ingredient and HPC to a compression force of 12,000 lb. (gauge) at 149°C for 1-4 min. The film is cooled under pressure by having cold water circulate in the platen. The inserts are then individually cut from the film with a rod-shaped punch. Each insert is placed in a vial, which is then placed in a humidity cabinet (88% relative humidity at 30°C) for 2-4 days. After removal from the cabinet, the vials are capped and then autoclaved at 121°C for 0.5 hr.

The following are representative pharmaceutical dosage forms of the compounds of Formula II:



the inhibitor. This technique may be used with a variety of enzymes, for example:

	Acid Phosphatase	Furin
	Activated Protein C	γ -Glutamyltranspeptidase
5	Alkaline Phosphatase	Granzymes A & B
	Aminopeptidases B & M	HIV Protease
	Amyloid A4-Generating Enzyme	IL-1B Convertase
	Angiotensinase	Kallikrein
	Aryl Sulfatase	Lysozyme
10	β -Galactosidase	Mast Cell Protease
	β -Glucosidase	Peroxidase
	β -Glucuronidase	Plasmin
	Calpains I & II	Prohormone Convertase
	Cathepsins B, C, D, & G	rANP Precursor Processing Enzyme
15	Cholinesterase	Renin
	Chymotrypsin	Spleen Fibrinolytic Proteinase
	Collagenase	Staphylocoagulase
	Dipeptidyl Peptidases I- IV	Thrombin
	Elastase	Tissue Plasminogen Activator
20	Endothelin Converting Enzyme	Trypsin
	Factor Xa	Tryptase
	Factor XIa	Urokinase
	Factor XIIa Df-Protease	

25 A bead lawn assay for testing carbonic anhydrase inhibition preferably comprises agarose for both layers, bovine carbonic anhydrase, and fluorescein diacetate.

30 Bead Lawn Assay (Carbonic Anhydrase). Beads to be tested are arrayed in a minimal amount of methanol in a 60 mm polystyrene tissue culture dish and then all the methanol allowed to evaporate. A 2.5% (wt./vol.) mixture of agarose (SeaPlaque, FMC BioProducts, Rockland, ME) in 20 mM sodium phosphate buffer (pH 7.4) is heated on a hot plate until the agarose dissolves and then is equilibrated to 37°C in a water bath. A separate stock of the same buffer is also equilibrated to 37°C. The enzyme layer is prepared as follows: 100 μ L of a bovine carbonic anhydrase stock (0.5 mg/mL or 53 μ M based on absorbance at 280 nm, Sigma #C-3934) is added to 2.15 mL of buffer, and 1.25 mL agarose solution is added to the mixture. The agarose/enzyme solution is poured onto the dish



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containing the beads and the agarose is allowed to solidify at r.t. for 3-5 min. To identify zones of inhibition, the compounds, which are optionally photoeluted by exposure to 4.7-6 mW/cm² 365 nm UV light for 5 sec. to 1 hr., are overlayed with fluorescein diacetate (FLDA,

5 Molecular Probes, Eugene, OR), which is prepared as follows: to 2.25 mL phosphate buffer is added 10 µL FLDA stock (10 mM in DMF at -20°C) and 1.25 mL agarose (final FLDA concentration: 30 µM). The solution is mixed thoroughly then poured over the enzyme layer in the dish. Zones of inhibition appear after 1-2 min. and intensify over 30-

10 45 min. They are dark against a yellow-green background when illuminated by short-wave UV light ($\lambda_{\text{max}} = 254 \text{ nm}$).

Bead Lawn Assay (Inositol Monophosphatase). The assay is similar to that for carbonic anhydrase, with the following substitutions: The buffer used is 20 mM Tris, 1 mM EGTA, pH 7.8.

15 The enzyme layer contains 1 mg/mL recombinant human inositol monophosphatase (purified from *E. coli*) and 10 mM MgCl₂. Three alternative substrates are used: methylumbelliferyl phosphate (Sigma, M-8883), a fluorogenic substrate, detected using filters around $\lambda_{\text{ex}} = 388 \text{ nm}$ and $\lambda_{\text{em}} = 420 \text{ nm}$; or CSPD or CDP-Star (chemiluminescent

20 substrates for alkaline phosphatase, Tropix, Bedford MA), detected directly without requiring filters. The preferred substrate is CSPD.



Methods of Synthesis

The compounds of the present invention can be prepared according to the following methods. At each step in the synthesis each solid support upon which a compound is being synthesized is uniquely

5 tagged to define the particular chemical event(s) occurring during that step. The tagging is accomplished using identifiers such as those of Formula IV, which record the sequential events to which the support is exposed during the synthesis, thus providing a reaction history for the compound produced on each support. The identifiers are used in

10 combination with one another to form a binary or higher order encoding scheme permitting a relatively small number of identifiers to encode a relatively large number of reaction products. For example, when used in a binary code, N identifiers can encode up to 2^N different compounds and/or conditions. By associating each variable or

15 combination of variables at each step of the synthesis with a combination of identifiers which uniquely define the chosen variables such as reactant, reagent, reaction conditions, or combinations of these, one can use the identifiers to define the reaction history of each solid support.

20 In carrying out the syntheses, one begins with at least 10^3 , desirably at least 10^4 , and generally not exceeding 10^{15} solid supports. Depending on the pre-determined number of R^1/R^2 choices for the first step, one divides the supports accordingly into as many containers. The appropriate reagents and reaction conditions are applied to each

25 container and the combination of identifiers which encode for each R^1/R^2 choice is added and attached. Depending on the chemistries involved, the tagging may be done prior to, concomitantly with, or after the reactions which comprise each choice. As a control, sample supports may be picked at any stage and a portion of their tags detached

30 and decoded to verify that the correct tags are bound to the sample supports. As needed, one may wash the beads free of any excess reagents or by-products before proceeding. At the end of each step, the supports are usually combined, mixed, and again divided, this time into as many containers as pre determined for the number of choices for the

35 second step in the synthesis. This procedure of dividing, reacting,



tagging, and remixing is repeated until the combinatorial synthesis is completed.

Scheme 1

Functionalized supports such as amino-functionalized or hydroxy-terminating PEG grafted polystyrene beads are divided into a pre-determined number of reaction vessels and are reacted with a cleavable linker/ligand element 3, which has been pre-formed, to generate 4. Unique tagging of the supports in each reaction vessel is achieved with combinations of identifiers encoded in a binary scheme, e.g., as depicted in Table 1-1 for three choices of R¹ and R². The identifiers are attached by adding a solution of the identifiers (in a 1.5% wt./wt. identifier:solid support ratio) to a batch of supports suspended in CH₂Cl₂ and shaking the mixture for 30 min. A dilute solution of rhodium trifluoroacetate dimer is added and the mixture is immediately shaken 4 hr and washed in CH₂Cl₂. The procedure is repeated and the mixture shaken for 14 hr and then washed in DMF/DCM.

Scheme 2

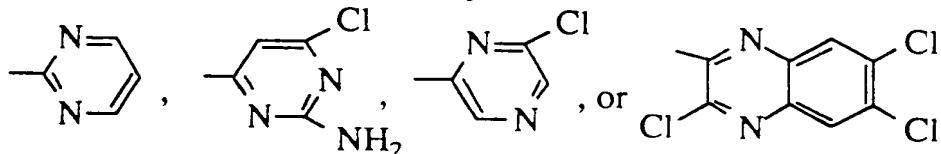
The compounds 4 are pooled, mixed, and divided into a pre-determined number of reaction vessels, each of which is treated with one reagent corresponding to ligand element =CR⁴R⁵, in the presence of pyrrolidine to produce 5a, 5b, and 5c. Unique tagging of the supports in each reaction vessel is achieved with combinations of additional identifiers encoded in a binary scheme, e.g., as depicted in Table 1-2 for seven choices of R⁴R⁵.

Scheme 3

The compounds 5c, where R⁴/R⁵/X represents the residue of piperidine, pyrrolidine, or aminocyclohexane, are pooled, mixed, and then divided into a pre-determined number of reaction vessels. The supports in each reaction vessel are uniquely tagged with combinations of additional identifiers encoded in a binary scheme, e.g., as depicted in Table 1-3 for 30 choices of R⁸ and in Table 1-5 for six choices of R¹⁴ and four choices of heteroaryl groups. After removal of any N-



protecting Boc group in R^4R^5 , each reaction vessel is treated with one reagent corresponding to ligand element R^8 in the presence of solvents such as CH_2Cl_2 , DMF, or EtOH and, when required, bases such as triethylamine or 2,6-lutidine to produce 6 having an R^8 substituent at 5 C-2 and a ketone at C-4, i.e., when R^6R^7 together are O. In Scheme 3, R^{14} is benzyl, - CH_2 -Ph-4-F, - CH_2 -Ph-4-OCH₃, - CH_2 -4-Py, n-pentyl, or - CH_2 -c-propyl; and heteroaryl is



Scheme 4

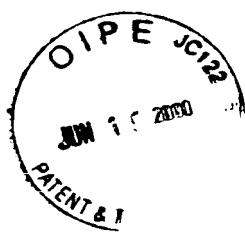
10 A portion of the compounds 5a, 5b, 5c, and 6 may be pooled, mixed, and then divided into a pre-determined number of reaction vessels where they may be uniquely tagged with combinations of additional identifiers encoded in a binary scheme, e.g., as in Table 1-4 for three choices of R^6/R^7 . Each vessel is treated with sodium borohydride to yield 7 as an alcohol at C-4 or is treated with 1,2-dithioethane and a Lewis acid such as $BF_3 \cdot Et_2O$ to yield 8 as a dithiolane at C-4, or is treated with an appropriate non-beta branched primary amine in the presence of $NaCNBH_3$ in MeOH, optionally with acetic acid, to yield secondary amine 9, or is left untreated.

15 Compounds 5a, 5b, 5c, 5d, 6, 7, 8, and 9 are then exposed to UV light (~360 nm) in polar solvents such as DMSO, H₂O, or a lower alkanol such as MeOH to cleave the compounds of Formula II from the support/linker complex.

Scheme 5

20 TentaGel resin may be modified with bis-Boc Lysine to increase the available reaction sites for ligand attachment Bis-Boc-lysine in DMF, HOEt, and DIC are shaken at r.t. and then dry TentaGel resin is added. The mixture is shaken at r.t. for 17 hr and then washed alternately with methanol and DCM and then with THF and dried

25 under vacuum. To deprotect the resin, DCM is added, followed by a 30 % TFA solution in DCM (100 mL). The vessel is shaken at room temperature for 15 min. before adding neat TFA.. The vessel is shaken



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at room temperature for 2.5 hr at which time the resin is washed with DCM, then treated with a solution of 10% triethylamine in DCM, then washed with DCM and DMF.

For purposes of simplicity, the schemes do not show the
5 use of this bis modification.

Scheme 6

Functionalized supports such as amino-functionalized or hydroxy-terminating PEG grafted polystyrene beads are divided into a pre-determined number of reaction vessels and are reacted with a
10 cleavable linker/ligand element 10, which has been pre-formed, to generate 11. Unique tagging of the supports in each reaction vessel is achieved with combinations of identifiers encoded in a binary scheme, e.g., as depicted in Table 2-1 for seven choices of -(CH₂)₁₋₆R¹⁷. The identifiers are attached by adding a solution of the identifiers (in a 7%
15 wt./wt. identifier:solid support ratio) to each batch of supports suspended in EtOAc and shaking the mixture for 1 hr. A dilute solution of rhodium trifluoroacetate dimer in DCM is added and the mixture is shaken 15 hr and washed with DCM (4X) and EtOAc (2X). The procedure is repeated for each identifier.

20 To deprotect the encoded resin, it is suspended in DCM and then agitated with a TFA solution in DCM. The resin is then washed with DCM followed by treatment with triethylamine in DCM and then washed with DCM.

Scheme 7

25 The compounds 12 are pooled, mixed, and divided into a pre-determined number of reaction vessels, each of which is treated with one acetophenone reagent corresponding to ligand element R², in the presence of DIC, HOBt, and DMF to produce 4'. Unique tagging of the supports in each reaction vessel is achieved with combinations of
30 additional identifiers encoded in a binary scheme analogous to that in Table 2-1.

Scheme 8

The compounds 4' are mixed, pooled, and divided into a predetermined number of reaction vessels, each of which is treated with

and aldehyde or ketone element corresponding to R⁴/R⁵ in the presence of pyrrolidine in methanol at 75°C to produce the compounds 5a', 5b', and 5c'. Unique tagging of the supports in each reaction vessel is achieved with combinations of additional identifiers encoded in a binary scheme analogous to that in Table 2-1.

Scheme 9

The compounds 5c', where R⁴/R⁵/X represents the residue of t-Boc protected piperidine, t-Boc protected aminocyclohexane, or other amine functionalized molecules are mixed, pooled, and divided

10 into a predetermined number of reaction vessels. The supports in each reaction vessel are uniquely tagged with combinations of additional identifiers encoded in a binary scheme analogous to that in Table 2-1. After removal of any N-protecting group in R⁴/R⁵, each vessel is treated with one reagent such as a chloroformate, isocyanate,

15 thioisocyanate, carboxylic acid, alkyl or aryl sulfonyl halide, aldehyde, or a haloheteroaromatic compound corresponding to ligand element R⁸ in the presence of solvents such as CH₂Cl₂, DMF, EtOH, or methanol. When required, bases such as triethylamine, DBU, or 2,6-lutidine and/or other reagents or combinations of reagents such as DIC,

20 NaCNBH₃, HOBt, and acetic acid are added to produce 6', having an R⁸ substituent at C-2 and a ketone at C-4, i.e. when R⁶R⁷ together are O.

Scheme 10

A portion of compounds 5a', 5b', 5c', and 6' may be pooled, mixed, and then divided into a pre-determined number of

25 reaction vessels where they may be uniquely tagged with combinations of additional identifiers encoded in a binary scheme analogous to that in Table 2-1. Each vessel is treated with 1) sodium borohydride in methanol to yield 7' as an alcohol at C-4; 2) 1,2-dithioethane and a Lewis acid such as boron trifluoride etherate to yield 8' as the dithiolane at C-4; 3) an unhindered primary amine along with NaCNBH₃ in acetic acid/methanol solvent at ca. 75°C to yield 9' as an amine at C-4; or 4) is left untreated.

Scheme 11

The compounds 9 or 9' are divided into a predetermined number of reaction vessels. Each vessel is treated with one reagent such as a chloroformate, isocyanate, thioisocyanate, carboxylic acid, alkyl or aryl sulfonyl halide, aldehyde, or a haloheteroaromatic compound corresponding to ligand element R¹⁵ in the presence of solvents such as CH₂Cl₂, DMF, EtOH, or methanol. When required, bases such as triethylamine, DBU, or 2,6-lutidine and/or other reagents or combinations of reagents such as DIC, NaCNBH₃, HOBr, and acetic acid are added to produce the corresponding compound 13 or 13'.

Scheme 12

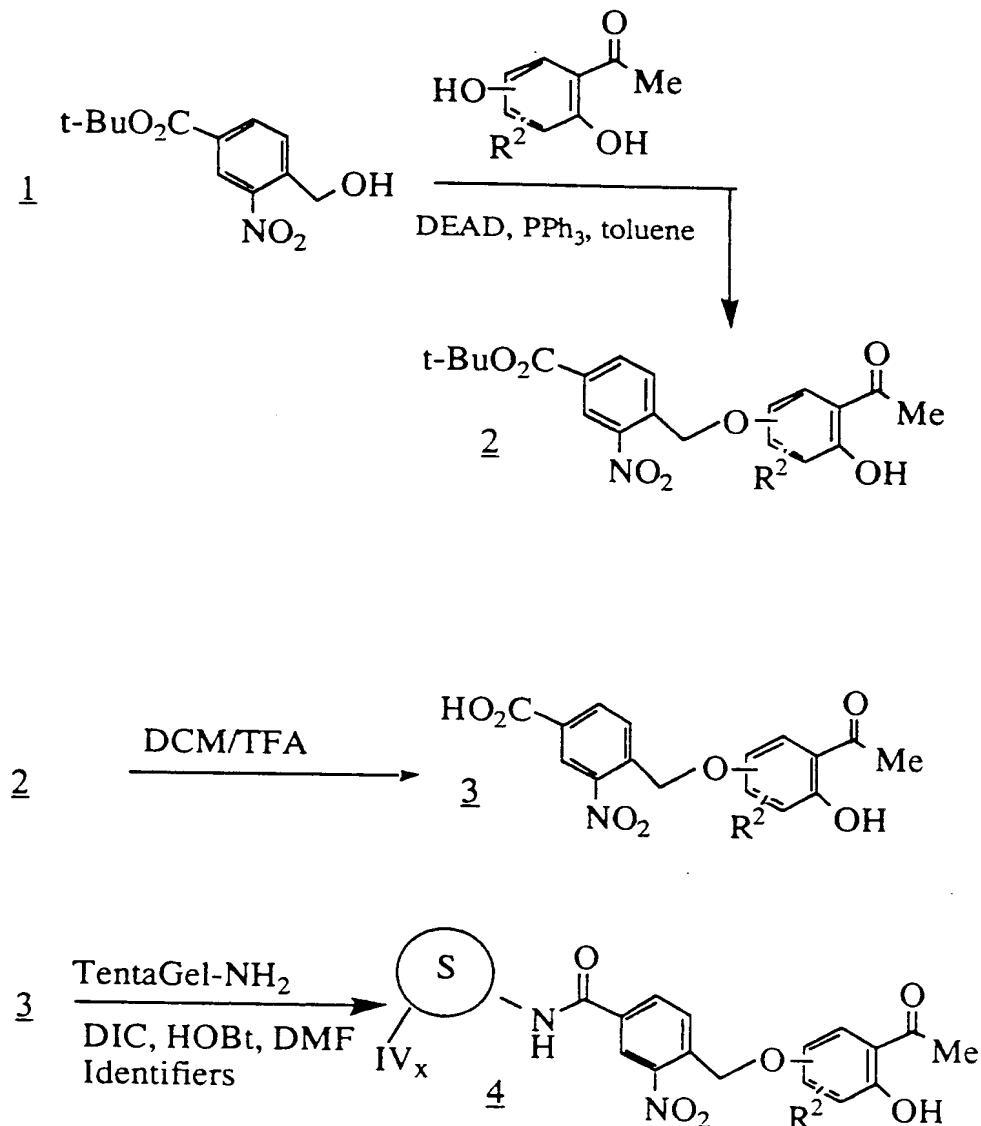
Functionalized supports such as amino-functionalized or hydroxy-terminating PEG grafted polystyrene beads are placed into a reaction vessel and are reacted with a cleavable linker/ligand element 10, which has been pre-formed, to generate 11'. To deprotect the resin, it is suspended in DCM and then agitated with a TFA solution in DCM. The resin is then washed with DCM followed by treatment with triethylamine in DCM and then washed with DCM to yield 12'.

In an appropriately sized synthesis vessel is placed HOBr (3 equiv.) and the carboxylic acid Q (X = OH) (3 equiv.) in a solvent such as DMF. DIC (3 equiv.) is added and the vessel agitated for 15 min. before adding the amino resin 12' (1 equiv. of amino sites). The resin is agitated for 5 hrs., then washed with alternating DCM and MeOH (5X each) and then with THF (2X) to yield 14.

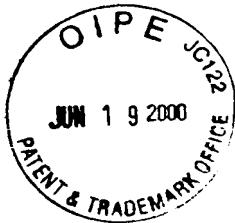
In an appropriately sized synthesis vessel is placed the amino resin 12' (1 equiv. of amino sites). A solvent such as DCM is added, followed by an organic base such as triethylamine, pyridine, Hünig's base (di-isopropylethylamine), or 2,6-lutidine (10 equiv.). The resin is agitated for 15 min. before adding the acid halide Q (X = Cl, Br) (5 equiv.) as a dilute solution in a solvent such as DCM. The resin is agitated for 4 hrs. and then washed with DCM and MeOH (5X each) to yield 14.



SCHEME 1
LINKER/1st LIGAND ELEMENT

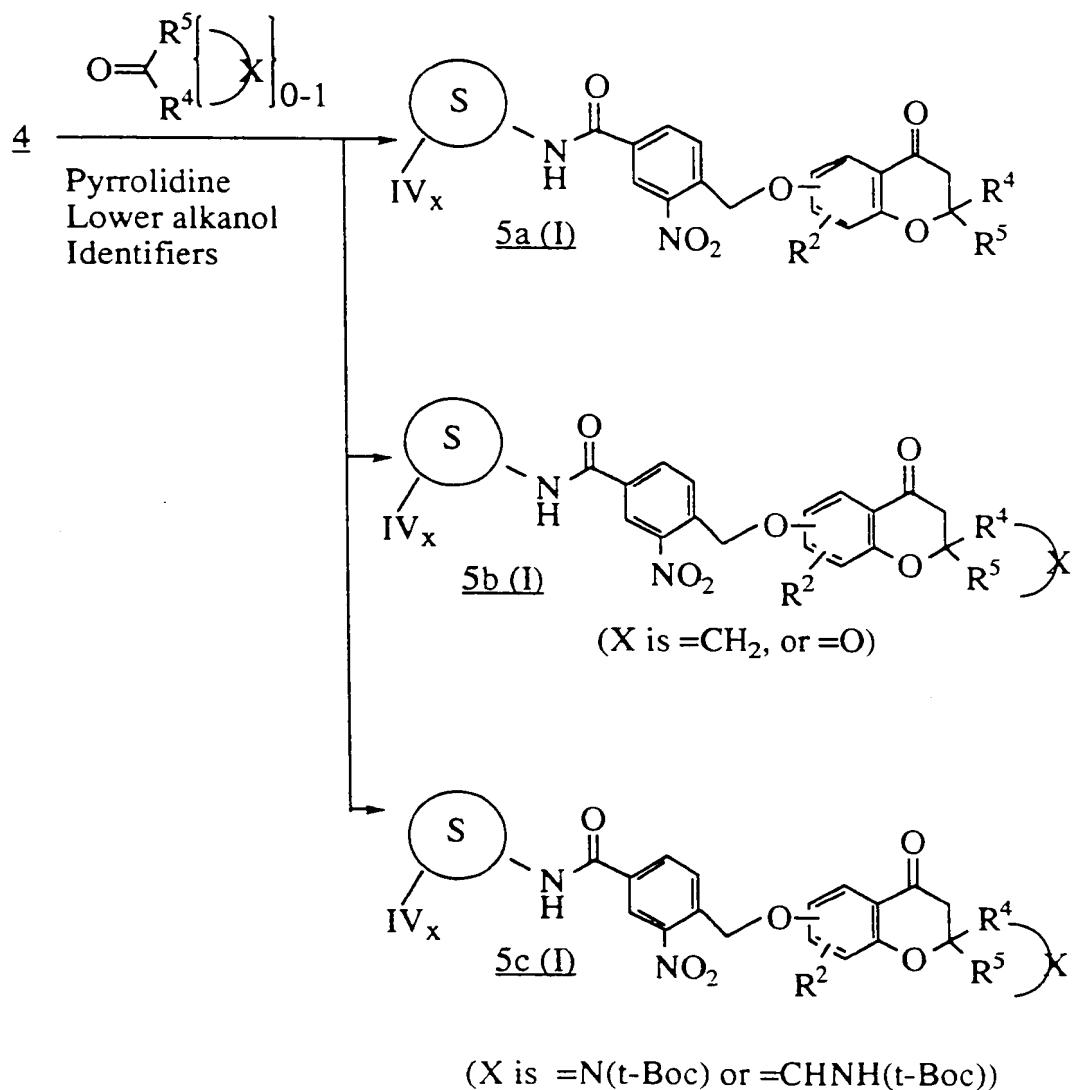


x is 1-30, depending on the binary code
for the selected solid support



SCHEME 2

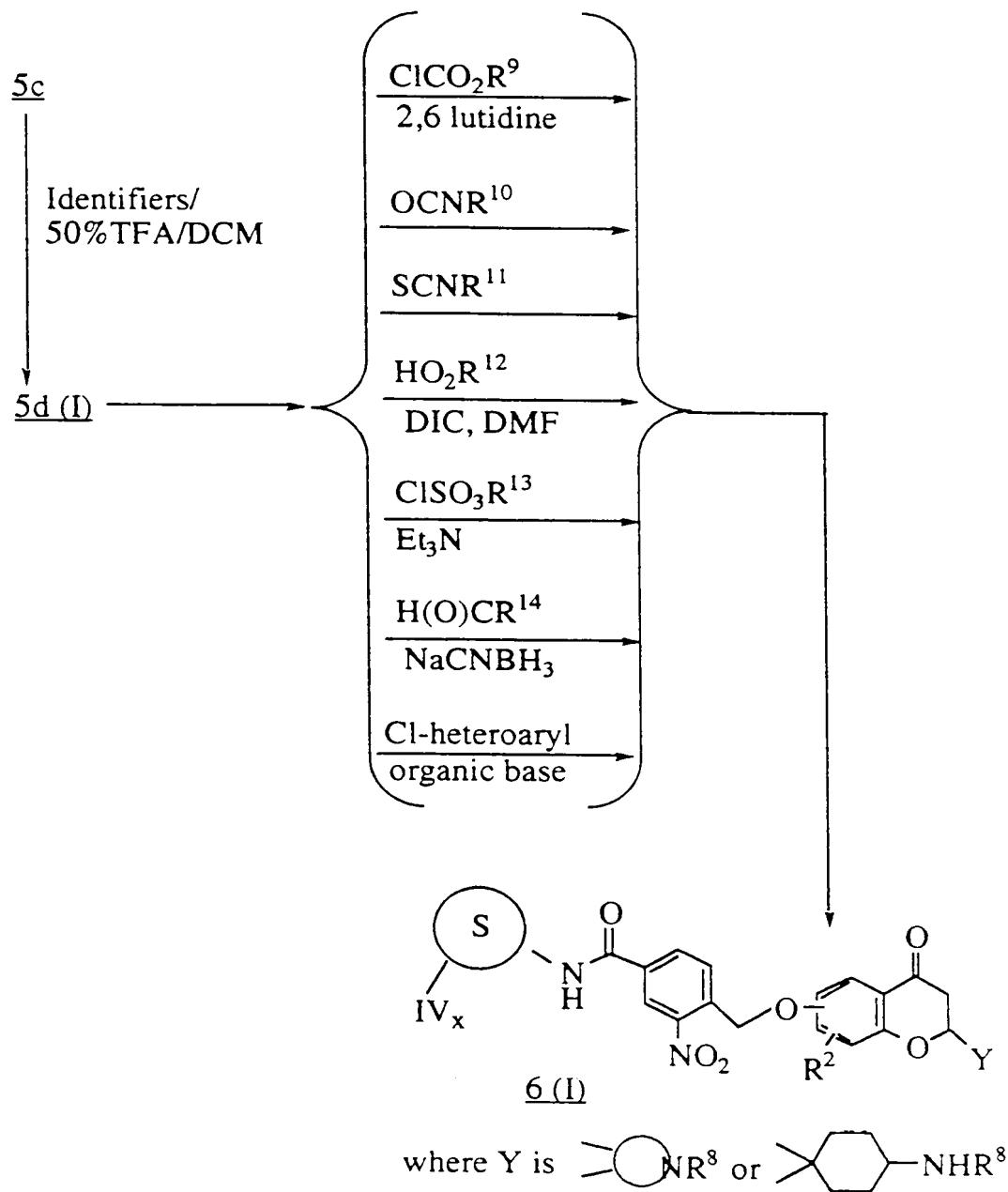
ADDITION OF R^4/R^5





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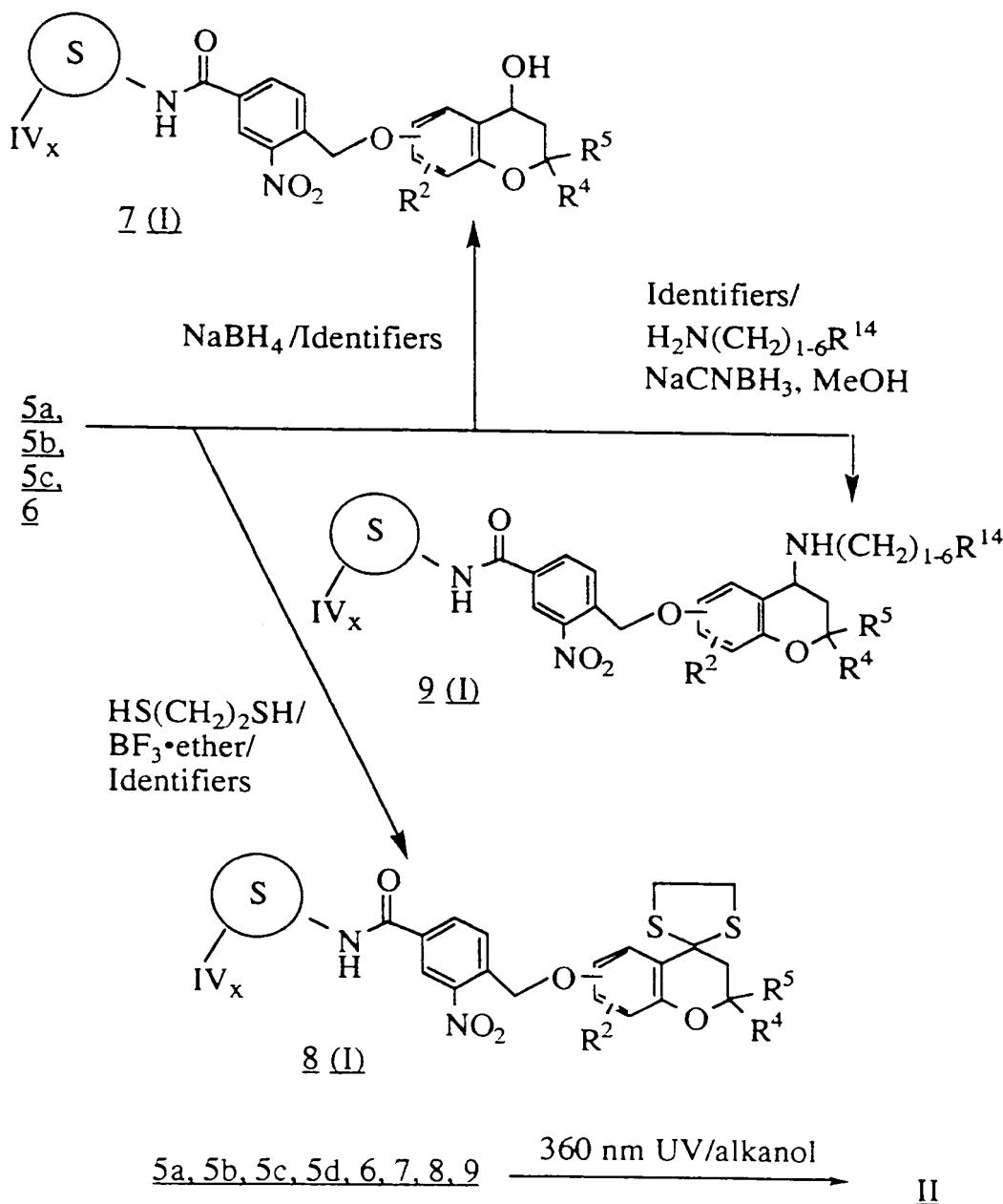
SCHEME 3
ADDITION OF R⁸





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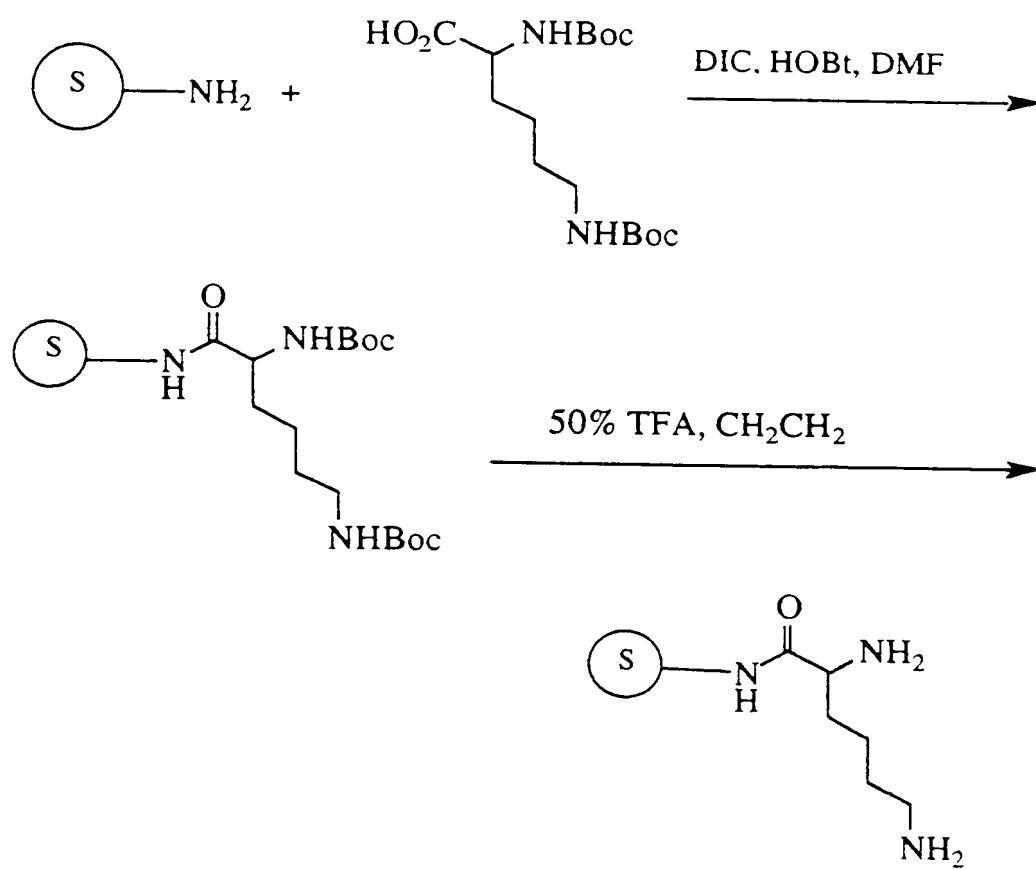
SCHEME 4
ADDITION OF R⁶/R7



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SCHEME 5
BIS-LINKER ATTACHMENT

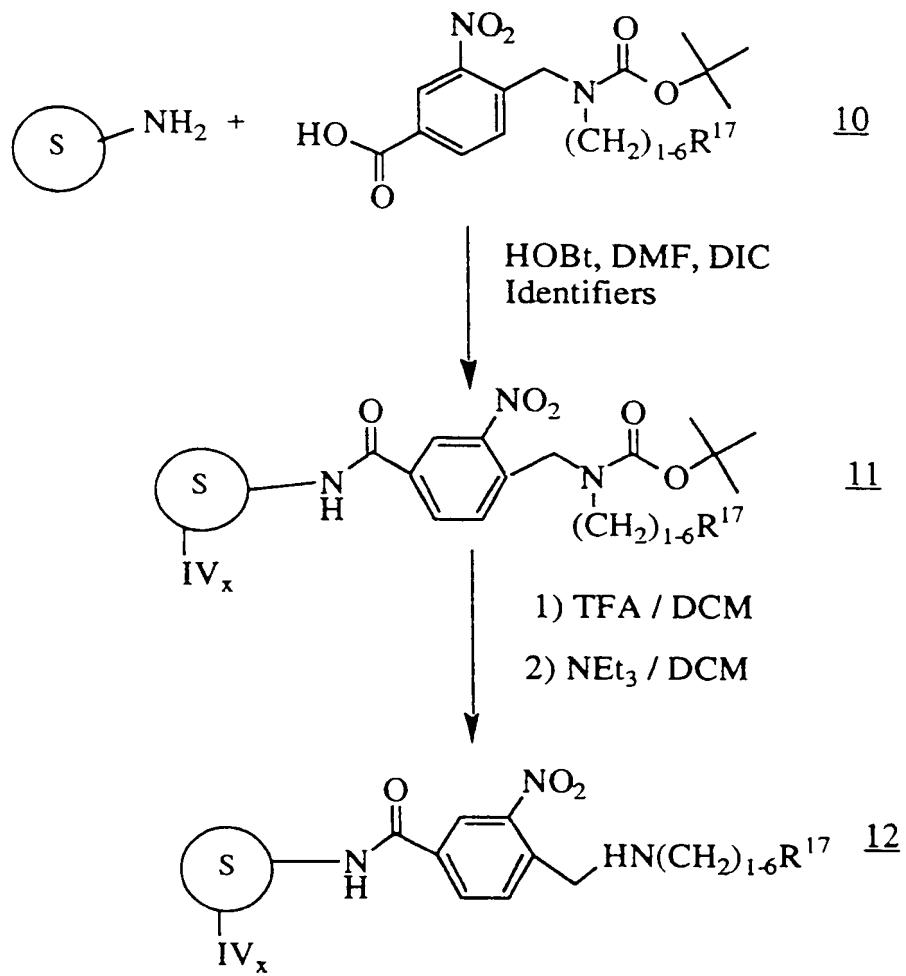


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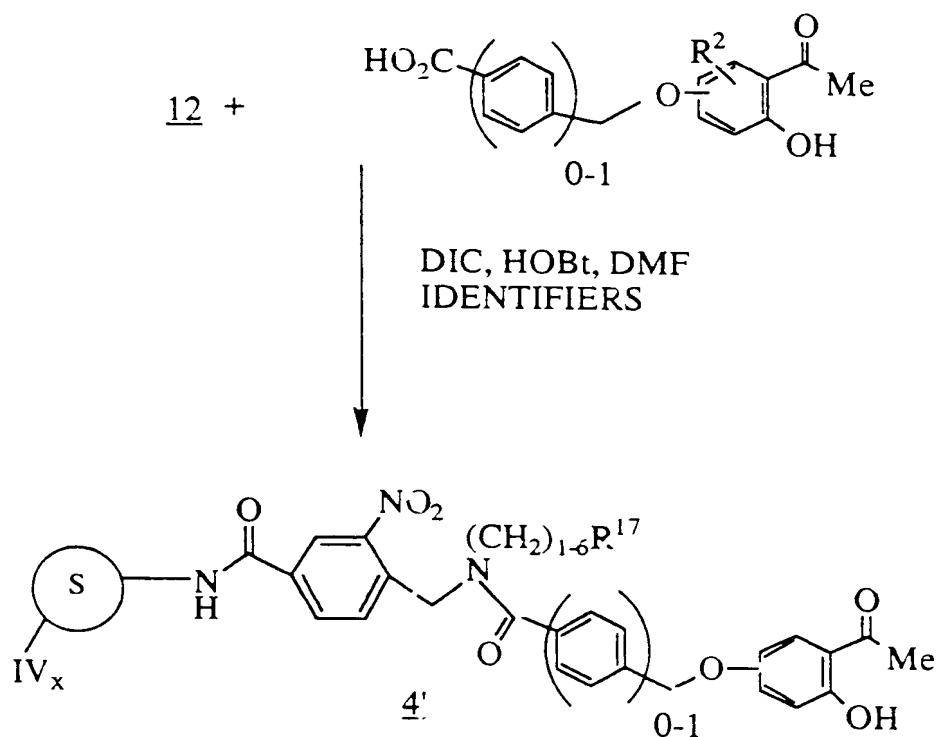
SCHEME 6

CLEAVABLE LINKER/1st LIGAND ELEMENT



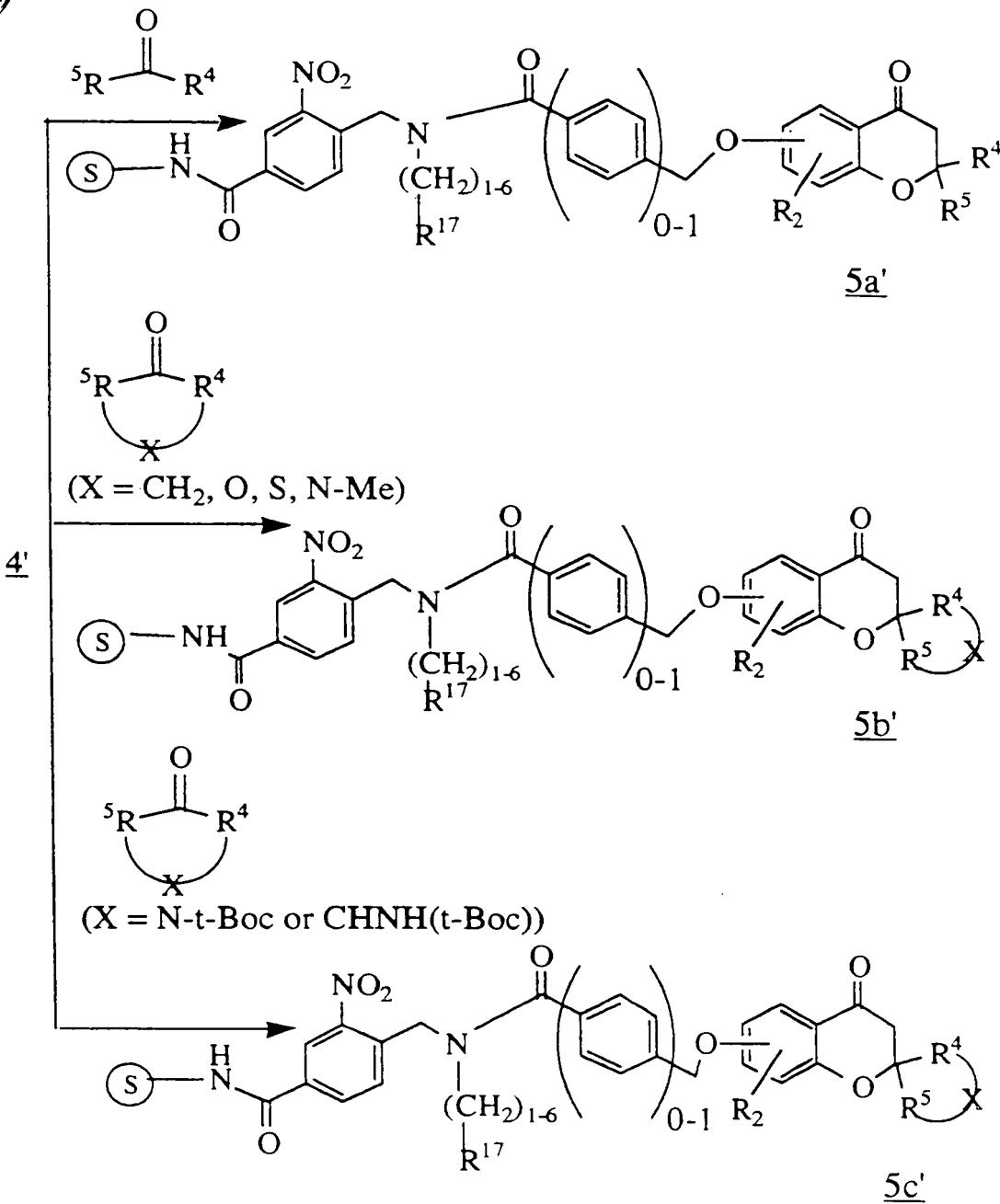
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SCHEME 7
ATTACHMENT OF HYDROXYACETOPHENONES



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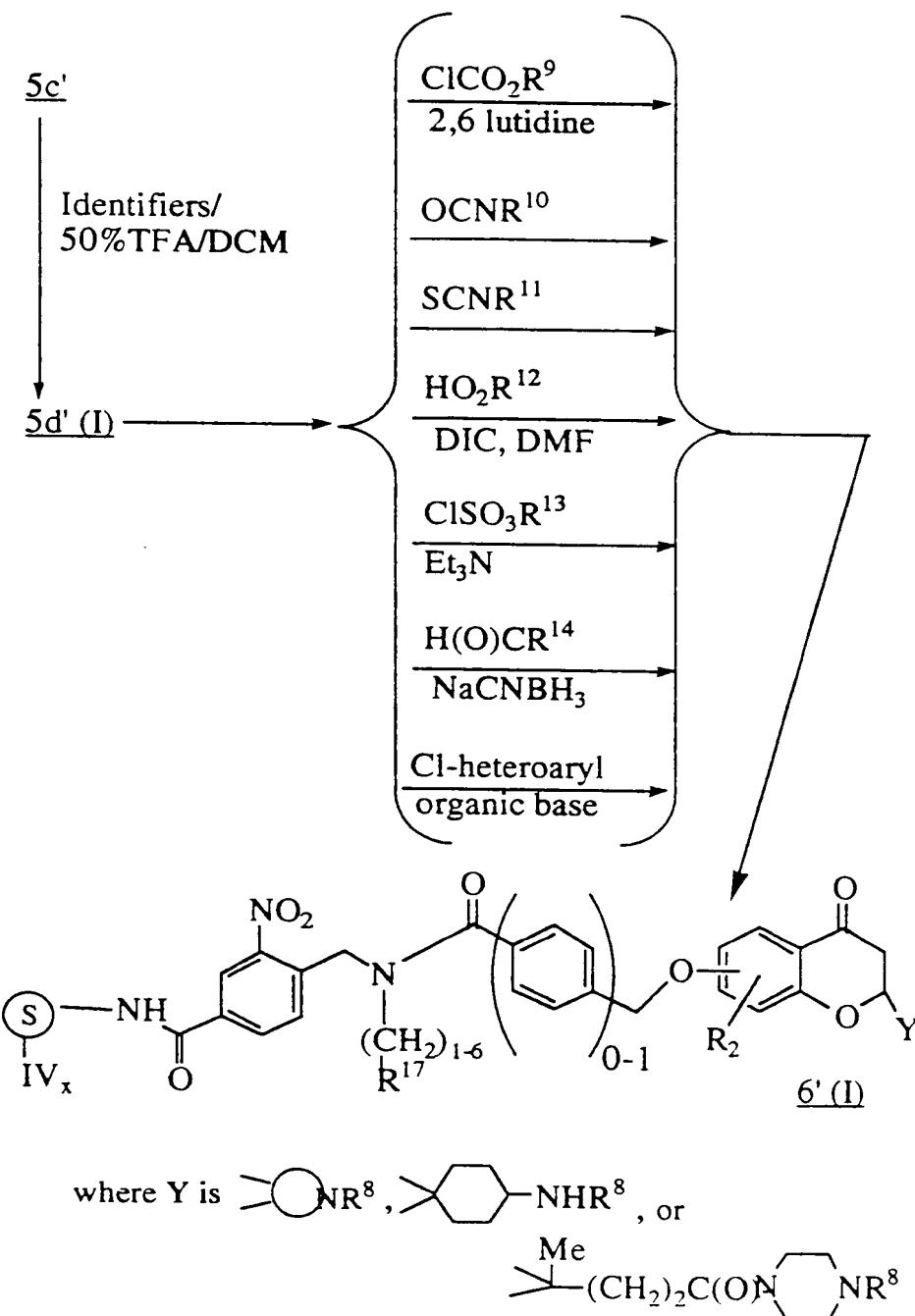
SCHEME 8
ADDITION OF R⁴/R⁵

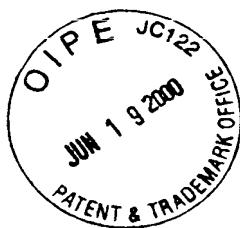




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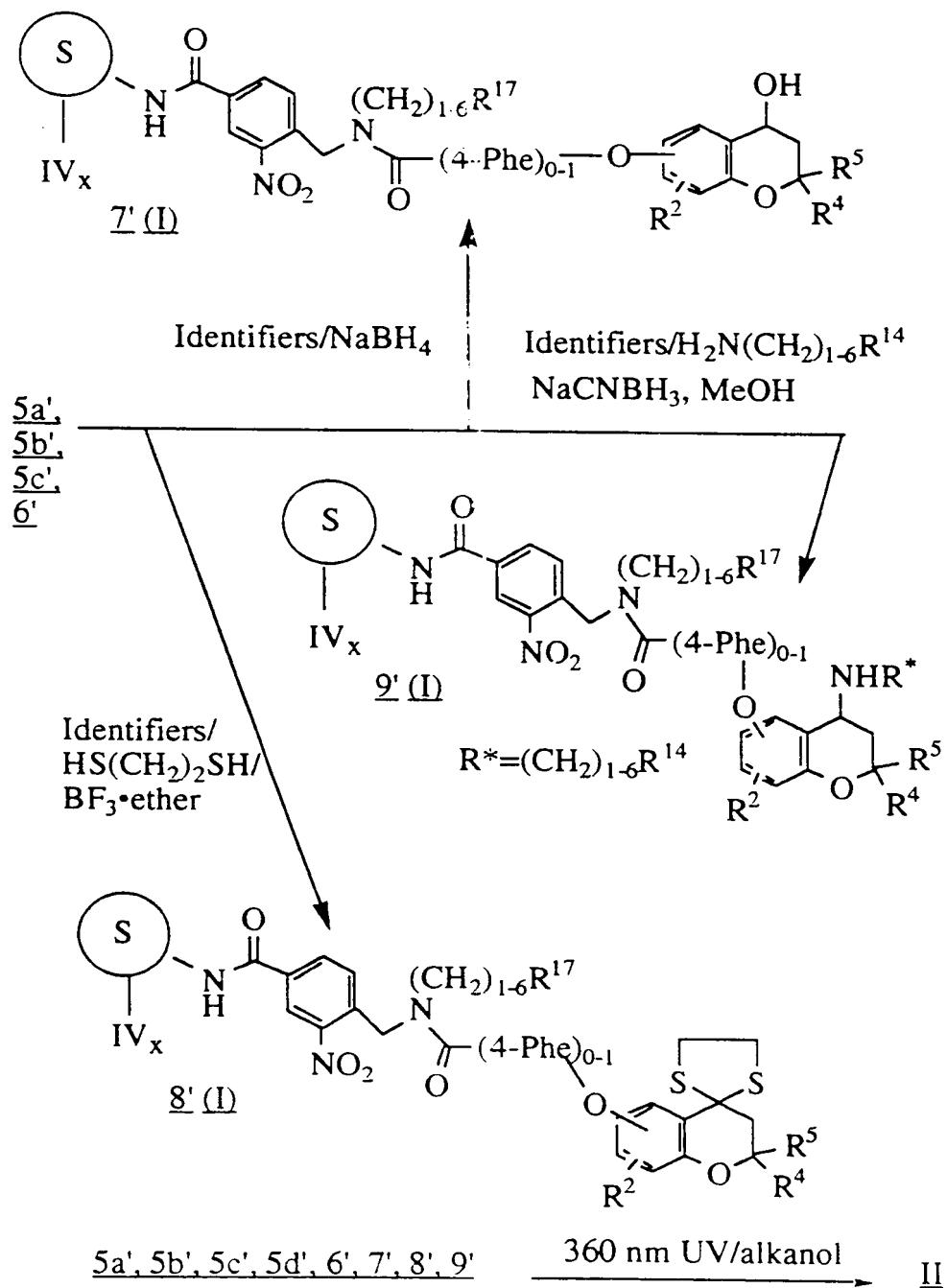
SCHEME 9
ADDITION OF R⁸





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SCHEME 10
ADDITION OF R⁶/R⁷



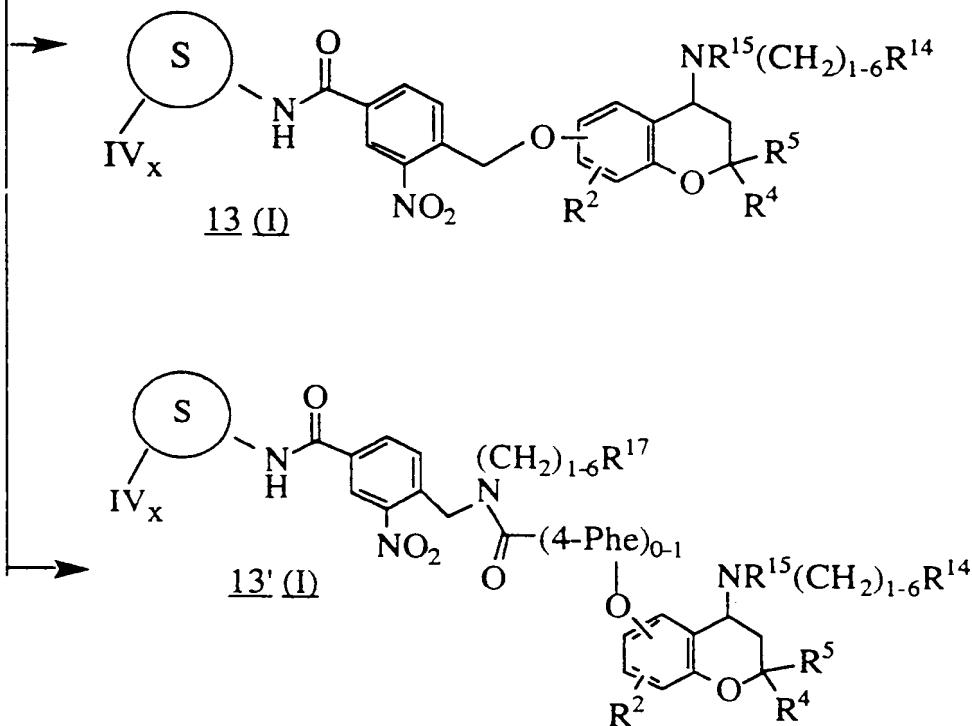


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SCHEME 11
ADDITION OF R¹⁵

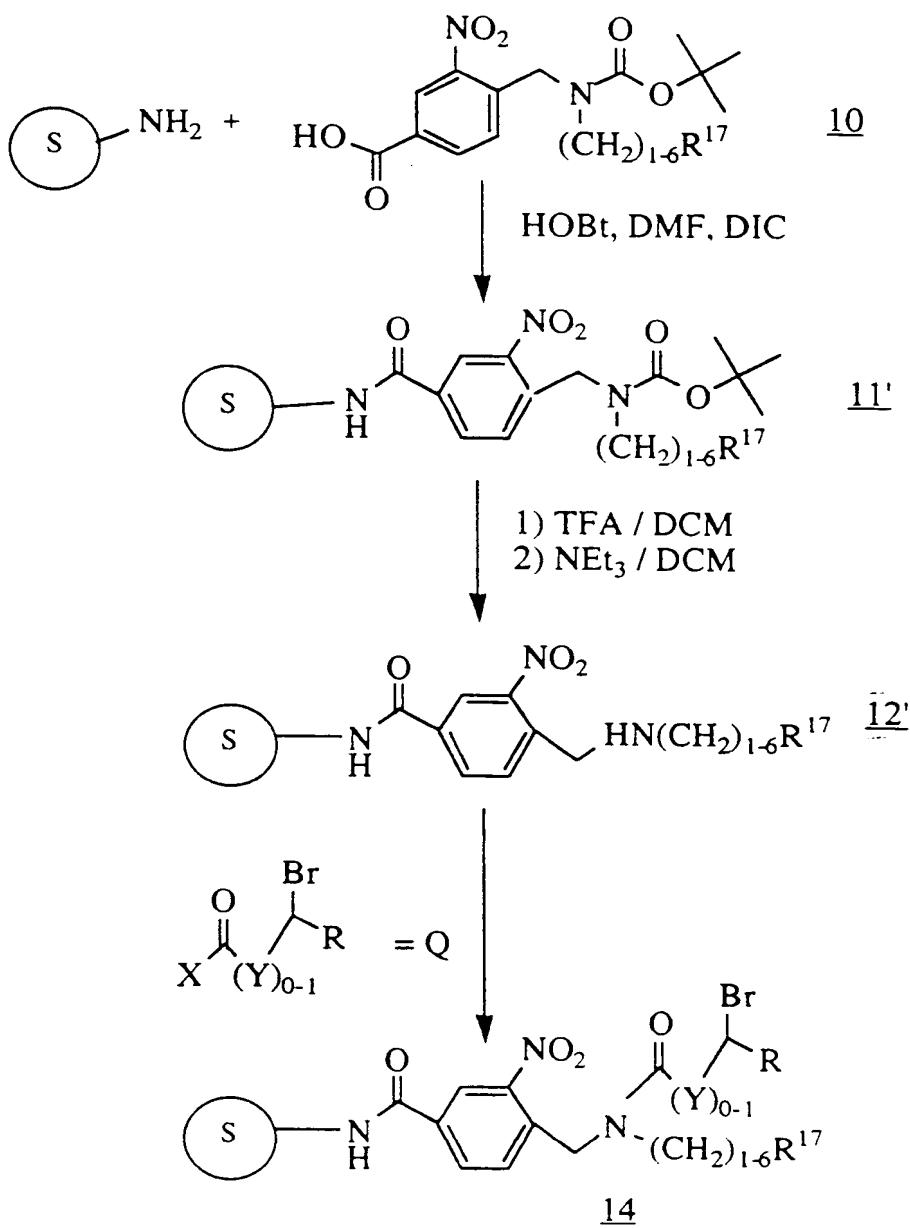
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Reagents as in Scheme 9





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SCHEME 12
COMBINATORIAL SYNTHONS

$\text{X} = \text{OH, Cl, Br}$
 $\text{Y} = \text{aryl, heteroaryl}$
 $\text{R} = \text{H, alkyl}$



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Table 2 illustrates compounds of Formula II which are representative of the present invention:

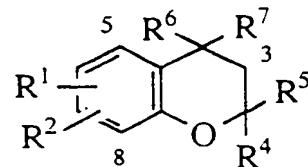


TABLE 2
REPRESENTATIVE COMPOUNDS

	R ¹	R ²	R ⁴	R ⁵	R ⁶	R ⁷
10	6-OH	8-CH ₃	C ₂ H ₅	C ₂ H ₅	OH	H
	7-OH	8-CH ₃	CH ₃	CH ₃	H	OH
	5-OH	7-CH ₂ H ₅	H	CH ₂ H ₅	NH ₂	H
15	6-O-(CH ₂) ₂ OH	H	C ₃ H ₇	CH ₃	=O	
	7-OCH ₂ CO ₂ H	H		-(CH ₂) ₄ -	H	morpholino
	8-O-(CH ₂) ₂ OH	H		-(CH ₂) ₅ -	N(CH ₃) ₂	H
	6-CO ₂ H	8-CH ₃		-(CH ₂) ₆ -	-S(CH ₂) ₂ S-	
	6-OH	H		-(CH ₂) ₂ O(CH ₂) ₂ -	=O	
20	7-OH	8-CH ₃	CH ₃	CH ₃	-S(CH ₂) ₂ S-	
	6-OH	H		-(CH ₂) ₅ -	=O	

25

30



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Table 3 illustrates additional compounds of Formula II representative of the present invention:

TABLE 3
REPRESENTATIVE COMPOUNDS

	R ¹	R ²	R ^{3/R⁴}	R ⁶	R ⁷	R ⁸
5	6-OH	H	-(CH ₂) ₂ NR ⁸ - (CH ₂) ₂ -	OH	H	-CONH-Ph-4-CF ₃
10	7-OH	8-CH ₃	-CH ₂ NR ⁸ - (CH ₂) ₃ -	-N SO ₂	H	-SO ₂ -2-Naph
15	5-O(CH ₂) ₂ OH	7-C ₂ H ₅	-(CH ₂) ₂ NR ⁸ - CH ₂ -	-N	H	-CSNH-Ph
20	6-OH	H	-(CH ₂) ₂ NR ⁸ - (CH ₂) ₂ -	=O		-CO-Ph-4-SO ₂ NH ₂
25	7-OH	H	-(CH ₂) ₂ CH- (NR ⁸)(CH ₂) ₂ -	-S(CH ₂) ₂ S-		-CO-Ph-4-SO ₂ NH ₂
30	6-OH	H	-(CH ₂) ₂ NR ⁸ - (CH ₂) ₂ -	=O		-COCH ₂ Ph
	6-OH	H	-(CH ₂) ₂ NR ⁸ - CH ₂ -	-S(CH ₂) ₂ S-		-CO ₂ -2-Py
	7-OH	8-CH ₃	-(CH ₂) ₂ NR ⁸ - (CH ₂) ₂ -	-S(CH ₂) ₂ S-		-CO-Ph-4-SO ₂ NH ₂
	6-OH	H	-(CH ₂) ₂ NR ⁸ - CH ₂ -	-S(CH ₂) ₂ S-		-CO-Ph-4-SO ₂ NH ₂

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Table 3 (Cont.)

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	7-OH	H	$-(CH_2)_2NR^{8-}(CH_2)_2-$	=O	$-CO-Ph-4-SO_2NH_2$
5	6-OH	H	$-(CH_2)_2NR^{8-}(CH_2)_2-$	OH	H CONH-Ph-4-CF ₃
	7-OH	8-CH ₃	$-(CH_2)_2NR^{8-}CH_2-$	N(CH ₃) ₂	H -SO ₂ -2-Naph
10	5-O(CH ₂) ₂ OH	7-C ₂ H ₅	$-(CH_2)_2NR^{8-}CH_2-$	-SCH ₂ CH-(CH ₃)S-	H -CSNH-Ph
	6-OH	H	$-(CH_2)_2NR^{8-}(CH_2)_2-$	=O	$-CO-Ph-4-SO_2NH_2$
15	7-OH	H	$-(CH_2)_2NR^{8-}(CH_2)_2-$	-S(CH ₂) ₂ S-	$-CO-Ph-4-SO_2NH_2$
	6-OH	H	$-(CH_2)_2NR^{8-}(CH_2)_2-$	=O	COCH ₂ Ph
20	6-OH	H	$-(CH_2)_2NR^{8-}CH_2-$	-S(CH ₂) ₂ S-	$-CO_2-2-Py$
	7-OH	8-CH ₃	$-(CH_2)_2NR^{8-}(CH_2)_2-$	-S(CH ₂) ₂ S-	$-CO-Ph-4-SO_2NH_2$
25	6-OH	H	$-(CH_2)_2NR^{8-}CH_2-$	-S(CH ₂) ₂ S-	$-CO-Ph-4-SO_2NH_2$
	7-OH	H	$-(CH_2)_2NR^{8-}(CH_2)_2-$	=O	$-CO-Ph-4-SO_2NH_2$

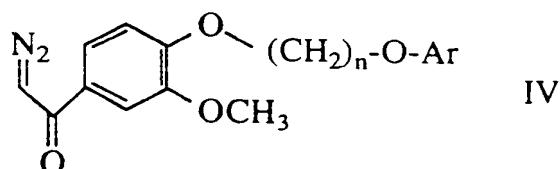


The invention is further defined by reference to the following examples, which are intended to be illustrative and not limiting.

5

PREPARATION 1 IDENTIFIERS

Twelve compounds of the general formula:



wherein:

10 n = 3-12 and Ar is pentachlorophenyl or
n = 5-6 and Ar is 2,4,6-trichlorophenyl
were prepared according to Scheme 13 and the following illustrative example.

15 a) Methyl vanillate (0.729 g, 4.0 mmol), 1-hydroxy-9-(2,3,4,5,6-pentachlorophenoxy)nonane (1.634 g, 4.0 mmol) and triphenylphosphine (1.258 g, 4.8 mmol) were dissolved in 20 mL dry toluene under argon. DEAD (0.76 mL, 0.836 g, 4.8 mmol) was added dropwise and the mixture was stirred at 25°C for one hr. The solution was concentrated to half volume and purified by flash chromatography
20 eluting with DCM to give 1.0 g (1.7 mmol, 43%) of the product as a white crystalline solid.

b) The methyl ester from Step (a) (1.0 g, 1.7 mmol) was dissolved in 50 mL THF, 2 mL water was added, followed by LiOH (1.2 g, 50 mmol). The mixture was stirred at 25°C for one hr. then
25 refluxed for 5 hr. After cooling to 25°C, the mixture was poured onto ethyl acetate (200 mL) and the solution was washed with 1 M HCl (3x 50 mL) then sat'd aq. NaCl (1x 50 mL) and dried over sodium sulfate. The solvent was removed and the crude acid azeotroped once with toluene. The crude material was dissolved in 100 mL toluene, 10 mL
30 (1.63 g, 14 mmol) thionyl chloride was added, and the mixture was refluxed for 90 min. The volume of the solution was reduced to



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approx. 30 mL by distillation, then the remaining toluene was removed by evaporation.

c) The crude acid chloride from Step (b) was dissolved in 20 mL dry DCM and cooled to -70°C under argon and a solution of 5 approx. 10 mmol diazomethane in 50 mL anhydrous ether was added. The mixture was warmed to r.t. and stirred for 90 min. Argon was bubbled through the solution for 10 min., then the solvents were removed by evaporation and the crude material was purified by flash chromatography, eluting with 10-20% ethyl acetate in hexane. The 10 diazoketone (0.85 g, 1.4 mmol, 82% yield over three steps) was obtained as a pale yellow solid.

In alternate Step (c) there is a change to the final diazo-methylation step, whereby the acid chloride is reacted with (trimethylsilyl)diazomethane and triethylamine to give the identifier, which can 15 then be used without further purification. With this alternate step, the identifier can be obtained in high yield with no chloromethylketone byproduct. Also, purification by flash chromatography is no longer necessary, which in some cases has resulted in significant acid-catalyzed 20 decomposition of the identifier.

Alternate Step c). To a solution of the acid chloride (3.8 mmol, 1.00 equiv.) and 1.85 mL (13.3 mmol, 3.50 equiv.) of triethylamine in anhydrous THF/acetonitrile (1:1) at 0°C under argon was added 5.7 mL (11.4 mmol, 3.00 equiv.) of a 2.0 M solution of 25 (trimethylsilyl)diazomethane in hexanes. The resulting orange solution was stirred at 0°C for 2 hr, then at 25°C for 17 hr. (If a precipitate formed immediately upon addition of (trimethylsilyl)diazomethane, CH₂Cl₂ was added until the precipitate redissolved). EtOAc was added (250 mL), and the organic layer washed with saturated aq. NaHCO₃ 30 (100 mL) and H₂O (100 mL), then dried (anhydrous MgSO₄). Removal of the volatiles in vacuo gave the product as yellow crystals in 60-100% yield.

The other 11 identifiers of Formula IV were prepared by analogous synthetic routes, steps (a), (b), and (c).



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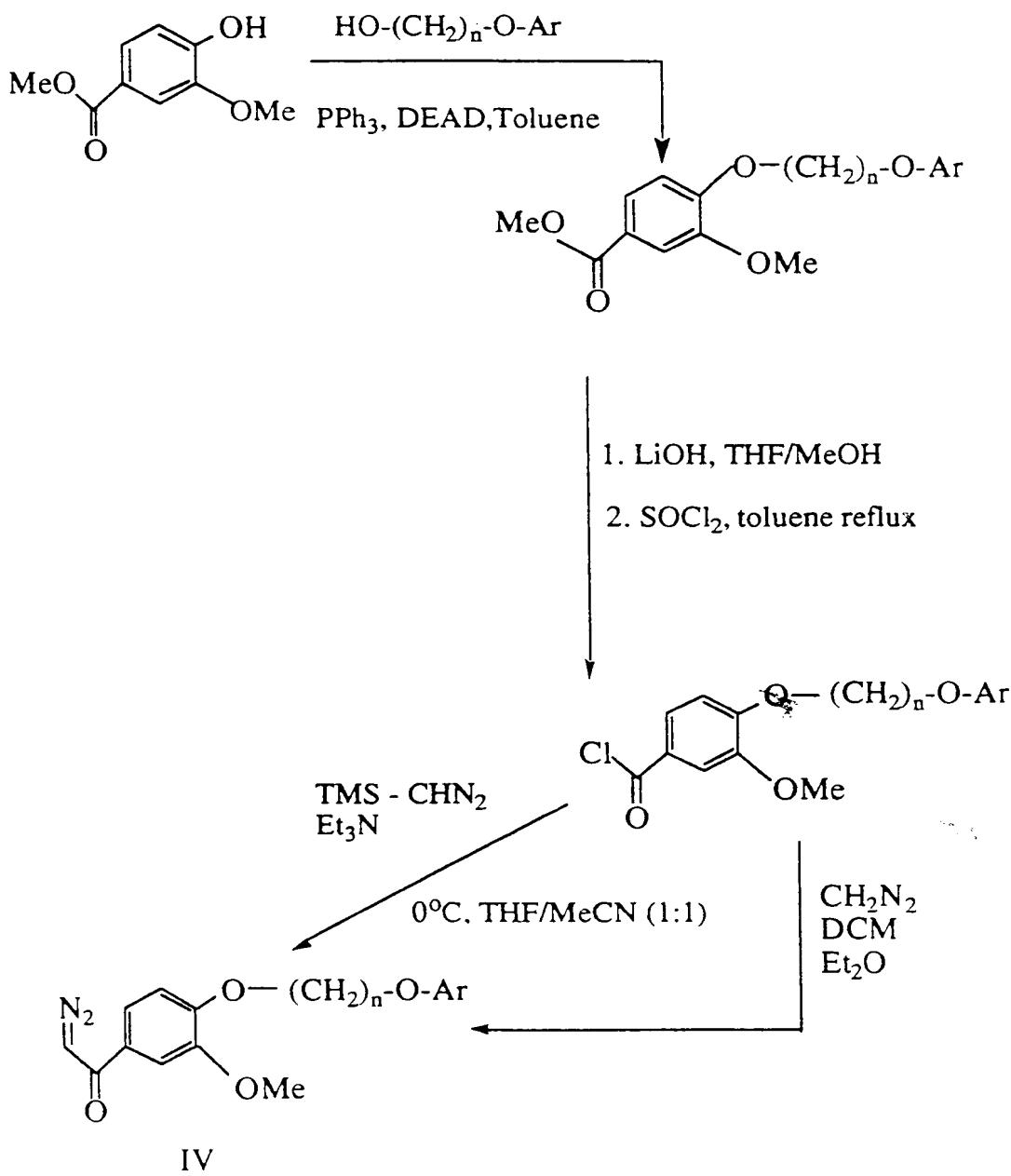
In the synthesis of Example 1, the 12 identifiers were used to encode the combinatorial library. In Step 1, pentachlorophenyl identifiers where $n = 11-12$ (abbreviated $C_{11}Cl_5$ and $C_{12}Cl_5$) were used in the following binary encoding scheme: $01 = (n = 12)$ and $10 = (n = 11)$. In Step 2, pentachlorophenyl identifiers where $n = 8-10$ (abbreviated C_8Cl_5 , C_9Cl_5 , and $C_{10}Cl_5$) were used and encoded as follows: $001 = (n = 10)$, $010 = (n = 9)$, and $100 = (n = 8)$. In Step 3, pentachlorophenyl identifiers where $n = 3-7$ (abbreviated C_3Cl_5 , C_4Cl_5 , C_5Cl_5 , C_6Cl_5 , and C_7Cl_5) were used and encoded as follows: $00001 = (n = 7)$, $00010 = (n = 6)$, $00100 = (n = 5)$, $01000 = (n = 4)$, and $10000 = (n = 3)$. In Step 4, trichlorophenyl identifiers where $n = 5-6$ (abbreviated C_5Cl_3 and C_6Cl_3) were used and encoded as follows: $01 = (n = 6)$ and $10 = (n = 5)$.

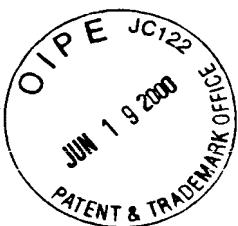
Thus, in Step 1 reagent 3 (Table 1-1) is encoded "11" which represents tagging this choice in the synthesis with the two pentachloro-phenyl identifiers where $n = 11$ and 12 .

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SCHEME 13 IDENTIFIERS





PREPARATION 2

t-BUTYL 4-(HYDROXYMETHYL)-3-NITROBENZOATE

5 t-Butyl 4-(acetoxymethyl)-3-nitrobenzoate was prepared as described by Barany and Albericio, *J. Am. Chem. Soc.* **1985**, *107*, 4936-4942. The reference's final procedure for hydrazinolysis of the acetate using hydrazine hydrate in CHCl₃ at 25°C produces only trace amounts of the desired hydroxymethyl final product, which is the t-butyl ester pre-cursor of the photocleavable linker used herein.

10 However, hydrazinolysis using hydrazine hydrate in MeOH at 25 °C produces t-butyl 4-(hydroxymethyl)-3-nitrobenzoate in high yield. Using MeOH as solvent, only the desired final product is obtained in near quantitative yield (93%).

15 t-Butyl 4-(hydroxymethyl)-3-nitrobenzoate: To a solution of 14.1 g (47.7 mmol, 1.00 equiv.) of t-butyl 4-(acetoxymethyl)-3-nitrobenzoate in MeOH (200 mL) was added 27.0 mL (477 mmol, 10.0 equiv.) of hydrazine hydrate (55% hydrazine). The resulting yellow solution was stirred at 25°C for 4 hr. EtOAc (250 mL) and saturated aq. NaCl (85 mL) were added, and the organic layer collected after shaking. The organic layer was washed further with saturated aq. NaCl (2 x 85 mL), and then dried (MgSO₄). Removal of volatiles *in vacuo* gave the product in 93% yield as yellow crystals.

20

PREPARATION 3

ALLYL 4-(HYDROXYMETHYL)-3-NITROBENZOATE

25 In a 100 mL round bottom flask was placed 4-hydroxymethyl-3-nitrobenzoic acid (1.97 g, 10 mmol). Allyl alcohol (20 mL) was added, followed by p-toluenesulfonic acid (0.190 g, 1 mmol). The mixture was heated to reflux for 24 hr., at which time all the volatiles were removed *in vacuo*. The residue was taken up in EtOAc and washed with sat'd KHCO₃. The organic layer was dried over MgSO₄ and concentrated to afford the title compound as a cream colored solid; 2.4 g (100%).



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PREPARATION 4
METHYL 4-(HYDROXYMETHYL)-3-NITROBENZOATE

Following the procedure of Preparation 3, but using methanol instead of allyl alcohol, the title compound was prepared in
 5 57% yield.

PREPARATION 5
BIS-LINKER MODIFIED RESIN

Step 1 Addition of bis-Boc lysine

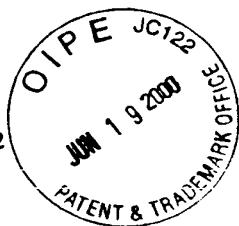
In a 250 mL synthesis vessel was placed bis-Boc-(L)-lysine
 10 (7.71g, 22.2 mmol) as a solution in DMF (150 mL). HOBt (2.84g, 21.0 mmol) was added followed by DIC (3.25 mL, 21.0 mmol) and the solution shaken at r.t for 15 min. before adding TentaGel resin (25.8 g, approximately 7.2 mmol amino sites). The mixture was shaken at r.t. for 17 hr and then washed alternately with methanol and DCM (5X each) and then with THF (2X) and dried under vacuum.

Step 2 Deprotection

Into each of seven 250 mL synthesis vessel was placed modified TentaGel resin (8.0 g, approx. 4.5 mmol of N-Boc amine sites). DCM (75 mL) was added followed by a 30 % TFA solution in DCM (100 mL). The vessel was shaken at room temperature for 15 min before adding neat TFA (15 mL). The vessel was shaken at room temperature for 2.5 hr at which time the resin was washed with DCM (2X). The resin was then treated with a solution of 10% triethylamine in DCM (2X150 mL) shaking for 20 min. each time. The resin was then washed with DCM (4X) and DMF (1X).

PREPARATION 6
t-Boc-PROTECTED AMINO ACID

In a 1 L flask was placed 3-nitro-4-(bromomethyl) benzoic acid (20.03 g, 77.0 mmol). THF (300 mL) was added followed by 4-methoxybenzylamine (10.0 mL, 77.0 mmol) and triethylamine (35 mL). The resulting clear solution was stirred at r.t. for 17.5 hr. Solid di-tert-butyl dicarbonate (16.8 g, 77.0 mmol) was added, followed by DMF (100 mL) and the resulting suspension stirred at r.t. for 72 hr.



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The reaction mixture was concentrated *in vacuo* and the residue taken up in ethyl acetate, washed with 1 N HCl (X2), dried (Na_2SO_4), filtered and concentrated to afford a dark brown oil. Purification *via* flash chromatography (ethyl acetate:hexane) resulted in a yellow foam which 5 was triturated with acetonitrile to give the expected protected amino acid (Table 2-1, compound 4) as a fine white powder (9.91g, 31%).

PREPARATION 7 t-Boc-PROTECTED AMINO ACID

Substantially following the procedure of Preparation 6, but 10 substituting the appropriate amine for 4-methoxybenzylamine, the remaining compounds of Table 2-1 are prepared.

EXAMPLE 1 1299 COMPOUND LIBRARY

15 Step 1

a) R^1/R^2

To a solution of t-butyl 4-hydroxymethyl-3-nitrobenzoate (2 g, 7.89 mmol, 1 equiv.), 2,4-dihydroxyacetophenone (1.20 g, 7.89 mmol, 1 equiv.), and triphenylphosphine (2.69 g, 10.26 mmol, 1.3 equiv.) in toluene (20 mL) was added dropwise DEAD (1.79 g, 10.26 mmol, 1.3 equiv.). After addition was complete the mixture was stirred for 16 hours at room temperature. The solvent was removed *in vacuo* and the residue was purified by flash chromatography (SiO_2 , eluted with 10% ethyl acetate in hexanes) affording 1.47 g of the product 25 (48% yield).

The t-butyl ester (500 mg, 1.29 mmol, 1 equiv.) above was dissolved/suspended in DCM (8 mL) and treated with TFA (3 mL). The mixture was stirred at room temperature for 8 hours. The DCM and TFA were removed *in vacuo* affording a white solid. This was 30 azeotroped once with toluene then dried *in vacuo* affording 427 mg (100% yield) of the carboxylic acid.

The acid (636 mg, 1.92 mmol, 1.5 equiv.) prepared above was dissolved in DMF (40 mL) and added to divinylbenzene-cross-linked, polyethyleneglycol-grafted polystyrene beads (TentaGel® S



NH₂, Rapp Polymere) (4.0 g, 0.32 mmol/g, 1.28 mmol, 1 equiv.) in a Merrifield reaction vessel. The resin was suspended by agitation, then HOEt (259 mg, 1.92 mmol, 1.5 equiv.) and DIC (0.31 mL, 1.92 mmol, 1.5 equiv.) were added in that order. The resin was agitated at room
5 temperature for 7 hours at which time it gave a negative Kaiser test. The resin was filtered and washed (DMF 3x50 mL, DCM 3x50 mL) then dried *in vacuo*.

10 The two other dihydroxyacetophenones were attached to the resin via the photocleavable linker in an analogous manner using the reagents of Table 1-1.

Alternate a)

In an analogous fashion the allyl and methyl esters were prepared from allyl 4-hydroxymethyl-3-nitrobenzoate (Preparation 3) and methyl 4-hydroxymethyl-3-nitrobenzoate (Preparation 4).

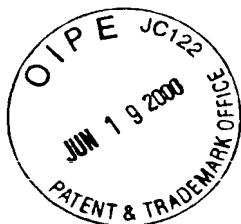
15 In a 10 mL flask was placed the allyl ester (110 mg, 0.3 mmol). Methylene chloride (2 mL) was added followed by tetrakis-triphenylphosphine palladium(0) (11.5 mg, 0.01 mmol) and the mixture cooled to 0°C. Pyrrolidine (50 mL, 0.6 mmol) was added and the reaction stirred at 0°C for 45 min. The mixture was diluted with
20 EtOAc (10 mL) and washed with 3.5N HCl. The organic layer was dried (MgSO₄), filtered, and concentrated to afford a yellow solid; 90.6 mg.

In an analogous manner the methyl ester was deprotected by basic hydrolysis using a mixture of dilute NaOH and THF.

25 b) Encoding of Step 1

Quantities of the three resin batches (2.5 g) from Step 1(a) were placed in separate synthesis vessels and each was suspended in DCM (20 mL). The three appropriate binary coding mixtures (Table 1-1) for each batch of resin were prepared by dissolving the
30 appropriate choice (37.5 mg) or choices (37.5 mg of each) of C₁₂Cl₅ and C₁₁Cl₅ -linker diazoketone (Preparation 1) in DCM (1 mL for each solution). These solutions were added to the appropriate synthesis vessel and the resin was agitated for 30 mins.

35 Rhodium trifluoroacetate dimer (1 mL of a 1 mg/mL solution in DCM) was added to each of the vessels and the resin was



agitated at room temperature for 4 hours. Each batch of resin was then filtered and washed with DCM (2x20 mL) then each was resuspended in DCM (20 mL) and treated a second time with the appropriate binary encoding mixture as described above. The resin was again agitated for
5 30 mins before addition of the rhodium trifluoroacetate dimer. The same quantities of catalyst and diazoketone compounds were used in the second coupling step as in the first. The resin was agitated for 14 hours. Each resin batch was then washed with DCM (5x20 mL) then the batches were combined and the entire library (three compounds)
10 was washed with DCM (10x50 mL).

Step 2.

a) Cyclocondensation Reactions

The dried resin from Step 1(b) was divided into four batches of 1.5 g (*ca.* 0.42 mmol) and three additional batches of 0.2g
15 (*ca.* 0.056 mmol). The 1.5g batches were placed into 25 mL round-bottomed flasks and the 0.2 g batches were placed into 5 mL round-bottomed flasks. The portions of resin were suspended in methanol (15 mL in the four flasks with 1.5 g of resin, 2 mL in the three flasks with 0.2 g of resin) and pyrrolidine (0.6 mL, 7.2 mmol, *ca.* 15 equiv. in the
20 flasks with 1.5 g of the resin; 0.08 mL, 0.96 mmol, *ca.* 15 equiv. in the flasks with 0.2 g of resin) was added to each flask. The reaction vessels were then allowed to stand for 5 min. to allow mixing of the reagents. The appropriate ketone (>10 equiv.) was then added to the vessels. The four BOC protected aminoketones were added to the flasks containing
25 1.5 g of resin and the other ketones were added to the flasks containing the 0.2 g of resin. The mixtures were heated at 75°C for 16 hr. The flasks were then cooled to room temperature and each batch of resin was poured into a separate sintered funnel and washed thoroughly with DMF (3x20 mL) and DCM (3x20 mL).

30 b) Encoding of Step 2

Each batch of resin from Step 2(a) was placed into a separate synthesis vessel and was suspended in DCM (5 mL for the batches of 1.5 g of resin, 1 mL for the batches containing 0.2 g of resin). The seven appropriate binary coding mixtures (see Table 1-2) for each batch of resin were prepared by dissolving the appropriate



choice (22.5 mg if added to a batch of 1.5 g of resin; 3.0 mg if added to a batch of 0.2 g of resin) or choices (22.5 mg of each if added to a batch of 1.5 g of resin; 3.0 mg of each if added to a batch of 0.2 g of resin) of C₁₀Cl₅, C₉Cl₅, and C₈Cl₅ linker-diazoketone (Preparation 1) in 5 DCM (1 mL for each solution). These solutions were added to the appropriate synthesis vessel and the resin was agitated for 30 mins.

Rhodium trifluoroacetate dimer (1 mL of a 1 mg/mL solution in DCM) was added to each of the vessels and the resin was agitated at room temperature for 4 hr. Each batch of resin was then 10 filtered and washed with DCM (2x20 mL) then each was resuspended in DCM (5 mL for the batches of 1.5 g of resin, 1 mL for the batches of 0.2 g of resin) and treated a second time with the appropriate binary encoding mixture as described above. The resin was again agitated for thirty mins before addition of the rhodium trifluoroacetate dimer. (The 15 same quantities of catalyst and diazoketone compounds were used in the second coupling step as in the first.) The resin was then agitated for 16 hr. Each resin batch was then washed with DCM (5x20 mL). The four batches of 1.5 g of resin were combined and washed with DCM (10x50 mL). These combined batches were then reacted further in Step 3.

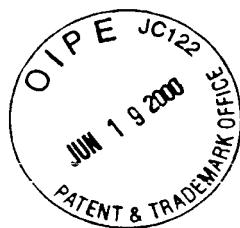
20 The three batches of 0.2 g of resin were combined and washed with DCM (10x20 mL). These combined batches were not used in Step 3 but were saved for Step 4.

Step 3

a) Encoding of Step 3

25 The four batches of 1.5 g of resin which had been combined in Step 2(b) were now divided into thirty lots of 170 mg each in 1 dram shell vials (Fisher Scientific) and each was suspended in DCM (2 mL). The thirty appropriate binary coding mixtures (see Table 1-3) for each batch of resin were prepared by dissolving the appropriate 30 choice (3 mg) or choices (3 mg of each) of C₇Cl₅, C₆Cl₅, C₅Cl₅, C₄Cl₅, and C₃Cl₅ linker-diazoketone (Preparation 1) in DCM (1 mL for each solution). These solutions were added to the appropriate synthesis vessel and the resin was agitated for 30 mins.

35 Rhodium trifluoroacetate dimer (1 mL of a 1 mg/mL solution in DCM) was added to each of the vessels and the resin was agitated at room temperature for 4 hr. The supernatant solution was



then decanted away from the resin with a Pasteur pipette. The resin was washed twice with DCM (3 mL) and the washings removed by Pasteur pipette. Each batch of resin was resuspended in DCM (2 mL) and treated a second time with the appropriate binary encoding mixture
5 as described above. The resin was again agitated for thirty minutes before addition of the rhodium trifluoroacetate dimer. (The same quantities of catalyst and diazoketone compounds were used in the second coupling step as in the first.) The batches of resin were then agitated for 16 hr. Each resin batch was then transferred to a small
10 Merrifield reaction vessel and washed with DCM (3x15 mL), DMF (2x15 mL), and DCM again (2x15 mL).

b) Deprotection

Each batch of resin was treated with a 50% solution of
15 TFA in DCM (6 mL:6 mL). The resin was agitated for 2 hr and then filtered and washed with DCM (3x15 mL). The resin was then treated with a 10% solution of triethylamine in DCM (1 mL:9 mL) and agitated for 10 mins. This treatment was repeated once. The resin was filtered and washed with DCM (4x10 mL).

20 c) Addition of R⁸

To each of the first six flasks was added DCM (5 mL) and the resin was agitated for 10 mins. 2,6-Lutidine (0.11 mL, 20 equiv.) was added to each flask followed by a solution of the appropriate
25 chloroformate (Table 1-3) in DCM (5 mL) and the resin was agitated for 4 hr. Except for isopropylchloroformate (Aldrich), the chloroformates were prepared from the appropriate alcohols by treating the alcohols (0.1 g) with a solution of phosgene in toluene (5 mL of a 1.8 M solution) for 1 hr, then evaporating to dryness *in vacuo*
30 , and then redissolving in DCM (5 mL).

To flasks 8, 9, and 10 was added ethanol (10 mL) and the appropriate isocyanate (Table 1-3) (0.1 mL, *ca.* 10 equiv.) and the resin was agitated for 4 hr.

To flasks 11, 12, and 13 was added ethanol (10 mL) and
35 the appropriate isothiocyanate (0.1 mL, 0.1 g of the naphthalene-isothiocyanate, *ca.* 10 equiv.) and the resin was agitated for 4 hr.



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To flasks 7 and 14-22 was added DMF (10 mL) and the appropriate carboxylic acid (*ca.* 10 equiv.) and HOBr (0.103 g, *ca.* 15 equiv.). The flasks were agitated for 30 mins then DIC (0.12 mL, *ca.* 15 equiv.) was added to each flask and the resin was agitated for 4 hr.

5 To flasks 23-30 was added DCM (10 mL) and triethylamine (0.15 mL, *ca.* 15 equiv.) and the resin was agitated for 15 mins. The appropriate sulfonyl chloride (*ca.* 10 equiv.) was added to the reaction vessels and the resin agitated for 4 hr.

10 The flasks were filtered and the resin washed with DCM (3x10 mL). All of the resin was combined in one large synthesis vessel and was washed with DCM (3x50 mL), DMF (3x50 mL), and DCM again (3x50 mL). The resin was dried *in vacuo*.

Alternative Step 3

a) Encoding of Alternative Step 3

15 The remaining 900 mg of resin from the four combined batches of 1.5 g from Step 2(b) which had not been used in Step 3 was divided into ten portions of 90 mg, and each portion placed in a separate 1 dram shell vial (Fisher Scientific). The ten appropriate binary coding mixtures (see Table 1-5) for each batch of resin were prepared by dissolving the appropriate choice (1.5 mg) or choices (1.5 mg each) of C₇Cl₅, C₅Cl₅, C₄Cl₅, and C₃Cl₅ linker-diazoketone (Preparation 1) in DCM (1 mL for each solution). These solutions were added to the appropriate synthesis vessels and the resin was agitated for 30 min.

20 25 Rhodium trifluoroacetate dimer (1 mL of a 1 mg/mL solution in DCM) was added to each of the vessels and the resin was agitated at room temperature for 4 hr. The supernatant solution was then decanted from the resin. The resin was washed (DCM 2x 3 mL) and the washings removed by Pasteur pipette. The resin was then treated a second time with solutions of the appropriate binary coding mixtures and agitated for 30 min. before the addition of the rhodium trifluoroacetate dimer. The same quantities of catalyst and diazoketone compounds were used in the second coupling as in the first. The batches of resin were then agitated for 16 hr. The resin was then transferred into small Merrifield synthesis vessels and washed (DCM 6x 15 mL).



b) Deprotection.

Each batch of resin was treated with a solution of TFA in DCM (4 mL:4 mL). The resin was agitated for 1 hr, then filtered and washed with DCM (2x 15 mL). The resin was then treated with a 5 solution of piperidine in DCM (4 mL:4 mL) and agitated for 15 min. This treatment was repeated once. Each batch of beads was washed with methanol (2x 15 mL) and DCM (4x 15 mL). Flasks 1-4 were washed with THF (3x 15 mL).

c) Heteroarylation Reactions

10 The resin in flasks 1-4 was suspended in THF (6 mL). Flasks 1-3 were then treated with DBU (190 μ L, ca. 40 equiv.) followed by the appropriate heteroaryl chloride (ca. 20 equiv.). Flasks 1 and 2 were heated at 55 °C for 16 hr. Flask 3 was heated at reflux for 16 hr. Flask 4 was treated with triethylamine (700 μ L) and the 15 appropriate heteroaryl chloride (ca. 20 equiv.). The resin was shaken at r.t. for 16 hr. Each batch of resin was then washed in THF (2x 15 mL) and dried *in vacuo*.

d) Reductive Alkylation

20 The resin in flasks 5-10 was suspended in DMF (8 mL) and the appropriate aldehyde (ca. 67 equiv.) added. Acetic acid (160 μ L) was added to each of the flasks followed by sodium cyanoborohydride (ca. 67 equiv.). Flasks 5, 6, 7, 9, and 10 were shaken at r.t. for 16 hr. Flask 8 was heated to 55 °C for 16 hr. Each batch of resin was filtered and washed with DMF (3x 15 mL). Each of the reductive alkylation 25 reactions was repeated under the same conditions. The batches of resin were washed with DMF (2x 15 mL), methanol (3x 15 mL), and DCM (3x 15 mL). The resin was then mixed, washed with DCM (2x 20 mL), and dried *in vacuo*.

30 This part of the library did not undergo further elaboration.

Step 4

a) Encoding of Step 4

To the combined resin from Step 3(c) was added 45 mg of resin from each of the seven flasks from Step 2(b) and the resin was 35 washed and mixed thoroughly with DCM (3x50 mL). From this



mixture was weighed out three portions of 800 mg of resin and these were placed into three separate Merrifield synthesis vessels and suspended in DCM (10 mL). The three appropriate binary coding mixtures (see Table 1-4) for each batch of resin were prepared by
5 dissolving the appropriate choice (24 mg) or choices (24 mg of each) of the C₆Cl₃ and C₅Cl₃ linker-diazoketone compound in DCM (1 mL for each solution). These solutions were added to the appropriate synthesis vessel and the resin was agitated for 30 mins.

Rhodium trifluoroacetate dimer (1 mL of a 1 mg/mL
10 solution in DCM) was added to each of the vessels and the resin was agitated at room temperature for 4 hr. Each batch of resin was then filtered and washed with DCM (2x20 mL) then each was resuspended in DCM (10 mL) and treated a second time with the appropriate binary encoding mixture as described above. The resin was again agitated for
15 30 mins before addition of the rhodium trifluoroacetate dimer. The same quantities of catalyst and diazoketone compounds were used in the second coupling step as in the first. The resin was agitated for 14 hr. Each resin batch was then washed with DCM (3x20 mL) and then filtered.
20

b) Carbonyl Reaction (addition of R⁶ and R⁷)

The resin in flask 1 was resuspended in DCM (6 mL) and 1,2-ethanedithiol (1 mL) and boron trifluoride etherate (1 mL) were added. The flask was shaken at room temperature for 6 hr. The resin
25 was then washed with DCM (20 mL) and then resuspended in DCM (6 mL) and treated once more with ethanedithiol (1 mL) and boron trifluoride etherate (1 mL). The resin was agitated at room temperature for 14 hr. The resin was then filtered and washed with DCM (5x20 mL).

30 The resin in flask 2 was suspended in methanol (5 mL) and solid sodium borohydride (200 mg) was added cautiously. The flask was vented and allowed to shake gently for 1 hr. The resin was filtered and resuspended in methanol and the reduction process repeated a total of 5 times at 1 hr intervals using 200 mg of sodium borohydride each time. After the final cycle the resin was washed with methanol (3x20 mL) and DCM (3x20 mL).
35

The resin in flask 3 was not reacted further.



The resin from the three flasks was combined and washed with DCM (5x50 mL) and then dried *in vacuo*. A portion (500 mg) of the resin was suspended in DCM (5 mL) and TFA (5 mL) and shaken for 2 hr. The resin was then treated twice with a 10% solution of 5 triethylamine in DCM (10 mL) and washed with DCM (5x20 mL). The resin was then dried *in vacuo*.

d) Decoding Procedure

A bead was placed in a 1.3 mm diameter pyrex capillary with 2 μ L of acetonitrile. Ceric ammonium nitrate solution (2 μ L of a 10 0.1 M aq.. solution) and hexane (3 μ L) were added and the two-phase mixture centrifuged briefly. The tube was sealed and left at 35 °C for 16 hrs, then opened. The organic layer was removed by syringe and mixed with 1 μ L of N,O-bis(trimethylsilyl)acetamide. The silated tag solution (1 μ L) was analyzed by GC with electron capture (EC) 15 detection.

The GC analysis was performed with a Hewlett Packard 5890 plus gas chromatograph. On column injection into a 5 m, 0.32 mm retention gap connected to a 25 m, 0.2 mm crosslinked 20 5% phenylmethyl silicone column was used. The temperature program was set at 200 °C for 1 min and then increased at a rate of 15°C/min from 200-320 °C. The pressure program was set at 20 psi for 1 min, then increased at 2 psi/min to 40 psi with a total run time of 10 min. The EC detector was maintained at 400 °C and the auxiliary gas was set at 35 psi.



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Table 1-1
R¹/R² Reagents and Encoding Scheme

<p>1. 01</p>	<p>2. 10</p>
<p>3. 11</p>	

Table 1-2

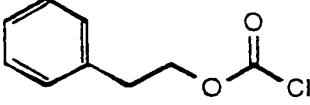
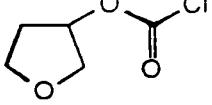
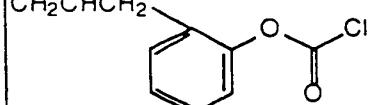
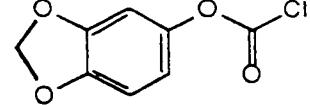
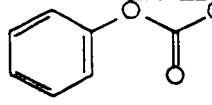
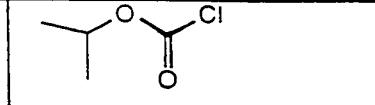
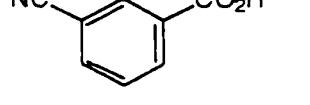
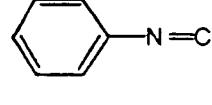
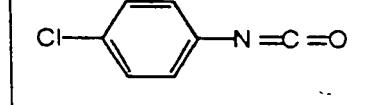
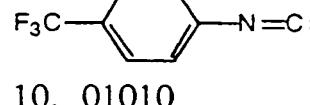
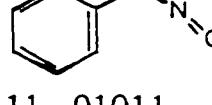
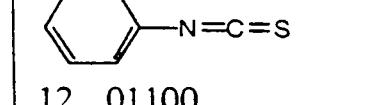
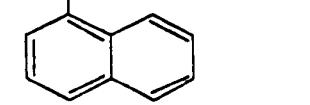
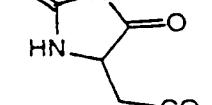
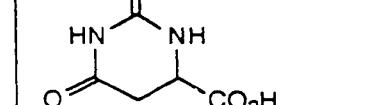
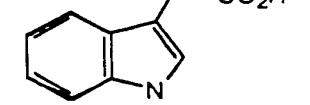
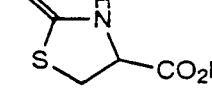
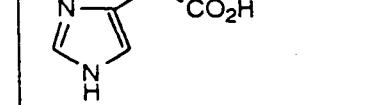
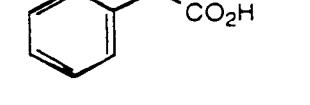
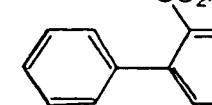
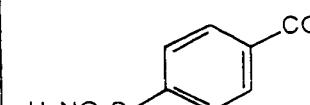
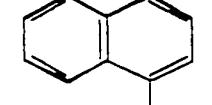
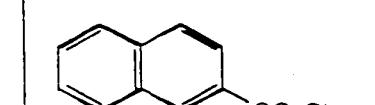
R⁴/R⁵ Reagents and Encoding Scheme

<p>1. 001</p>	<p>2. 010</p>	<p>3. 011</p>	<p>4. 100</p>
<p>5. 101</p>	<p>6. 110</p>	<p>7. 111</p>	



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Table 1-3
R⁸ Reagents and Encoding Scheme

		
5 1. 00001	2. 00010	3. 00011
		
10 4. 00100	5. 00101	6. 00110
		
15 7. 00111	8. 01000	9. 01001
		
20 10. 01010	11. 01011	12. 01100
		
25 13. 01101	14. 01110	16. 01111
		
30 16. 10000	17. 10001	18. 10010
		
35 19. 10011	20. 10100	21. 10101
		
30 22. 10110	23. 10111	24. 11100



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 25. 11001	 26. 11010	 27. 11011
 5 28. 11100	 29. 11101	 30. 11110

Table 1-4
R⁶/R⁷ Reagents and Encoding Scheme

10	/BF ₃ •OEt ₂ 1. 01	NaBH ₄ 2. 10	No reaction 3. 11
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Table 1-5
R⁸ and Heteroaryl Encoding Scheme

15	 1. 0001	 2. 0010
20	 3. 0011	 4. 0100
25	 5. 0101	 6. 0110
30	 7. 1000	 8. 1100
	 9. 1010	 10. 1001



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EXAMPLE 2
87,906 COMPOUND LIBRARY

Step 1

a) Addition of $(CH_2)_{1-6}R^{17}$

5 In a 250 mL synthesis vessel was placed the deprotected modified TentaGel resin (8.0 g, approx. 4.5 mmol of amine sites) from Preparation 5. HOEt (1.81g, 13.4 mmol) was added followed by the N-Boc-p-methoxybenzylamino acid (Table 2-1, compound 4) (5.60g, 13.4 mmol) and DMF (150 mL). The mixture was shaken at r.t. for 10 min.

10 before adding DIC (2.1 mL, 13.4 mmol). The mixture was shaken at r.t. for 16 hr and then washed alternately with methanol and DCM (4X each) and then with EtOAc (2X). Analysis of the resin via the standard Kaiser ninhydrin test indicated that the coupling reaction was complete.

15 In six separate vessels, analogous couplings were carried out with the six other Boc-protected amino acids listed in Table 2-1. All coupling reactions were repeated until satisfactory Kaiser ninhydrin test results were obtained (in all cases either one or two couplings).

b) Encoding of Step 1

20 While still in their separate 250 mL synthesis vessels, resin batches number 4, 5, 6, and 7 from Step 1 were suspended in EtOAc (100 mL). Into each of these four vessels was placed the Cl₅C₇-linker diazoketone (0.56 g) and the mixtures agitated for 1 hr. To each of the four vessels was then added rhodium trifluoroacetate dimer (6 mL of a 1 mg/mL solution in DCM) and the resin was agitated for 15 hr. The resin was then washed with DCM (4X) and EtOAc (2X).

25 In turn, the Cl₅C₈-linker diazoketone was applied to resin batches numbered 2, 3, 6, and 7 and the Cl₅C₁₁-linker diazoketone was applied to resin batches 1, 3, 5, and 7. Application of each tagging molecule was done separately and in analogous fashion to that of the Cl₅C₇-linker diazoketone outlined above. The seven batches of encoded resin were all combined in a 2 L Erlenmeyer flask along with THF (1 L) and mixed thoroughly by swirling and stirring gently with a glass rod. The resin was then recovered by filtration and vacuum dried.



Step 2: Addition of R²

a) Deprotection

5 In a 250 mL synthesis vessel is placed mixed, encoded resin from Step 1 (9 g) along with DCM (just enough to suspend resin). TFA (75 mL of a 30 % solution in DCM) is added and the resin agitated for 3.5 hr. The resin is then washed with DCM (2X) followed by treatment with 10% triethylamine in DCM (2X 20 min. each) and then washed with DCM (4X).

b) Coupling

10 The deprotected resin from Step 2(a) (9 g) is suspended in DMF (7 mL). HOBT (2.04 g, 15 mmol) is added followed by the acetophenone acid (Table 2-2, compound 3) (3.36g, 15 mmol) and the mixture agitated for 15 min. DIC (2.3 mL, 15 mmol) is added and the mixture agitated for 21 hr. The resin is washed alternately with DCM 15 and methanol (5X each) and then with EtOAc (4X).

In five separate vessels, analogous couplings are carried out with the five other acetophenone acids listed in Table 2-2.

c) Encoding of Step 2

20 The six batches of resin from Step 2 are binarily encoded in a fashion analogous to that described above for encoding of Step 1

The six batches of encoded resin are combined in a 2 L Erlenmeyer flask along with THF (1 L) and mixed thoroughly by swirling and stirring gently with a glass rod. The resin is then recovered by filtration and vacuum dried.

Step 3 Addition of R⁴R⁵

a) Cyclocondensation reactions

30 The mixed resin from Step 2 is divided into three batches of 14.4 g (*ca.* 8.1 mmol) and seven additional batches of 1.5 g (*ca.* 0.84 mmol). The 14.4 g batches are placed into 250 mL round bottom flasks and the 1.5 g batches are placed in 25 mL round bottom flasks. The portions of resin are suspended in methanol (150 mL in the three flasks with 14.4 g resin, 15 mL in the seven flasks with 1.5 g resin) and pyrrolidine (10.1 mL, 121 mmol, *ca.* 15 equiv. in the flasks with 14.4 g resin; 1.0 mL, 12.6 mmol, *ca.* 15 equiv. in the flasks with 1.5 g resin) is



added to each flask. The reaction vessels are then allowed to stand for 15 min. to allow mixing of the reagents. The appropriate ketone (5 to 10 equiv.) is then added to the vessels. The three Boc-protected aminoketones from Table 2-3 are added to the flasks containing 14.4 g

5 of resin and the seven other ketones, from Table 2-4, are added to the flasks containing 1.5 g of resin. The mixtures are heated at 75°C for 16 hr. The flasks are then cooled to r.t. and each batch of resin is poured into a separate synthesis vessel of appropriate size and washed thoroughly with DCM, DMF, and methanol (alternating: 5X each).

10

b) Encoding of Step 3

Each of the ten batches of resin from Step 3(a) is binarily encoded in a fashion analogous to that described for encoding Step 1.

c) Mixing and dividing

15

The seven 1.5 g batches of encoded resin are combined in a 500 mL Erlenmeyer flask along with THF (250 mL) and mixed thoroughly by swirling and stirring gently with a glass rod. The resin is then recovered by filtration and vacuum dried. This combined resin is kept separate from the three 14.4 g batches of resin and is not

20

subjected to the reaction conditions of Step 4, but rather re-divided into three 0.2 g portions and seven 1.4 g portions and saved to be used in Step 5 and alternate Step 5. The three 14.4 g batches of encoded resin are combined in a 2 L Erlenmeyer flask along with THF (1 L) and mixed thoroughly by swirling and stirring gently with a glass rod. The resin is then recovered by filtration, vacuum dried, and used in Step 4.

25

Step 4

a) Deprotection

30 Into each of seven 250 mL synthesis vessels is placed mixed, encoded resin from the three combined 14.4 g batches from Step 3 (6 g) along with DCM (just enough to suspend the resin). TFA (75 mL of a 30 % solution in DCM) is added and the resin agitated for 3.5 hr. The resin is then washed with DCM (2X) followed by treatment with 10% triethylamine in DCM (2X 20 min. each) and then washed with DCM (4X).



b) Nitrogen elaboration

In the first of the seven 250 mL synthesis vessels containing deprotected resin from Step 4(a) (6 g, ca. 3.4 mmol) is placed DCM (150 mL) and triethylamine (15 equiv.). Phenylsulfonyl chloride (ca. 5 10 equiv.) is added and the resin agitated for 4 hr. The resin is washed with alternating DCM and methanol (5X each) and then with EtOAc (2 X).

In the second of the seven 250 mL synthesis vessels containing deprotected resin from Step 4(a) (6 g, ca. 3.4 mmol) is 10 placed DCM (150 mL) and triethylamine (15 equiv.). Butyl chloride (ca. 10 equiv.) is added and the resin agitated for 4 hr. The resin is washed with alternating DCM and methanol (5X each) and then with EtOAc (2X).

In the third of the seven 250 mL synthesis vessels 15 containing deprotected resin from Step 4(a) (6 g, ca. 3.4 mmol) is placed DMF (150 mL) and HOBr (ca. 15 equiv.). 4-Carboxybenzenesulfonamide (ca. 10 equiv.) is added and the resin agitated for 30 min. DIC (ca. 10 equiv.) is added and the resin agitated for 4 hr. The resin is washed with alternating DCM and methanol (5X each) and 20 then with EtOAc (2X).

In the fourth of the seven 250 mL synthesis vessels containing deprotected resin from Step 4(a) (6 g, ca. 3.4 mmol) is 25 placed DMF (150 mL) and acetic acid (3 mL). Benzaldehyde (ca. 50 equiv.) is added and the resin agitated for 30 min. Sodium cyanoborohydride (ca. 50 equiv.) is added and the resin agitated for 16 hr. The resin is washed with alternating DCM and methanol (5X each) and then with EtOAc (2X).

In the fifth of the seven 250 mL synthesis vessels containing deprotected resin from Step 4(a) (6 g, ca. 3.4 mmol) is 30 placed DMF (150 mL) and acetic acid (3 mL). Butyraldehyde (ca. 50 equiv.) is added and the resin agitated for 30 min. Sodium cyanoborohydride (ca. 50 equiv.) is added and the resin agitated for 16 hr. The resin is washed with alternating DCM and methanol (5X each) and then with EtOAc (2X).

35 The resin from the sixth of the seven 250 mL synthesis vessels containing deprotected resin from Step 4(a) (6 g, ca. 3.4 mmol)



is transferred to a 250 mL round bottom flask. THF (150 mL) is added followed by DBU (*ca.* 40 equiv.). 2-Chloropyrimidine (*ca.* 20 equiv.) is added. The mixture is heated to 55°C for 16 hr. The resin is transferred back to a 250 mL synthesis vessel, washed with alternating
5 DCM and methanol (5X each), and then with EtOAc (2X).

In the seventh of the seven 250 mL synthesis vessels containing deprotected resin from Step 4(a) (6 g, *ca.* 3.4 mmol) is placed absolute ethanol (150 mL). Methyl isocyanate (*ca.* 15 equiv.) is added and the resin agitated for 12 hr. The resin is washed with
10 alternating DCM and methanol (5X each) and then with EtOAc (2X).

c) Encoding of Step 4

Each of the seven batches of resin from Step 4(b) are binarily encoded in a fashion analogous to that described for the encoding of Step 1.

15 The seven batches of encoded resin are combined in a 2 L Erlenmeyer flask along with THF (1 L) and mixed thoroughly by swirling and stirring gently with a glass rod. The resin is then recovered by filtration and vacuum dried. This resin is then divided into three batches of 0.7 g each and seven batches of 5.7 g each. The
20 seven 5.7 g. batches are subjected to Step 5. The three 0.7 g batches are subjected to alternate Step 5.

Step 5

a) Encoding

25 Each of the seven 5.7 g. batches of resin from Step 4(c) and the seven 1.4 g batches from Step 3(b) are binarily encoded in a fashion analogous to that described for the encoding of Step 1.

b) Reductive amination

30 The seven encoded 5.7 g. batches of resin from Step 5(a) are placed in 200 mL round bottom flasks. The seven encoded 1.4 g. batches from Step 3(c) are placed in 50 mL round bottom flasks. To each of the fourteen flasks is added a solution of 10% glacial acetic acid in methanol (60 mL in the 200 mL flasks, 15 mL in the 50 mL flasks). The appropriate amine from Table 2-6 (*ca.* 40 equiv.) is added followed by sodium cyanoborohydride (*ca.* 40 equiv.). Condensers are attached



and the mixtures are heated to 75°C for 48 hr. The resin is washed with alternating DCM and methanol (5X each) and then with EtOAc (2X).

Alternate Step 5

5 a) Thioketalization

One of the three 0.7 g. batches of resin from Step 4(c) and one of the 0.2 g batches of resin from Step 3(c) are placed in two separate 30 mL synthesis vessels. To each is added DCM (6 mL), followed by 1,2-ethanedithiol (1 mL) and boron trifluoride etherate (1 mL). The resin is agitated at r.t. for 6 hr. The resin is washed with DCM (1X) and then treated once more with ethanedithiol (1 mL) and boron trifluoride etherate (1 mL). The resin is agitated at r. t. for 14 hr. The resin is then filtered and washed with alternating DCM and methanol (5X each) and then with EtOAc (2X).

15 b) Reduction

One of the three 0.7 g. batches of resin from Step 4(c) and one of the 0.2 g batches of resin from Step 3(c) are placed in two separate 30 mL synthesis vessels. To each is added methanol (6 mL) and (cautiously) solid sodium borohydride (200 mg). The flasks are vented and allowed to gently shake for 1 hr. The resin is filtered and resuspended in methanol (6 mL) and the reduction process repeated a total of 5 times at 1 hr. intervals using 200 mg portions of sodium borohydride each time. After the final cycle, the resin is washed with alternating DCM and methanol (5X each) and then with EtOAc (2X).

25 c)

One of the three 0.7 g. batches of resin from Step 4(c) and one of the 0.2 g batches of resin from Step 3(c) is left unaltered.

Step 6

a) Mixing

30 The seven 5.7 g batches of encoded resin from Step 5(b) are combined in a 2 L Erlenmeyer flask along with THF (1 L). The seven 1.4 g batches of encoded resin from Step 5(b) are combined in a 500 mL Erlenmeyer flask. Each batch of resin is mixed thoroughly by



swirling and stirring gently with a glass rod. The resin from each flask is recovered by filtration, vacuum dried, and kept separate.

b) Nitrogen elaboration.

The mixed and dried resin from the combined 5.7 g. 5 batches in Step 6(a) (total of *ca.* 32.5 g.) is divided into ten 3.2 g. batches and placed in 100 mL synthesis vessels. The mixed and dried resin from the combined 1.4 g. batches in Step 6(a) (total of *ca.* 9.8 g.) is divided into ten 0.98 g. batches and placed in 30 mL synthesis vessels. These vessels are paired up into ten sets of two where each set has one 10 100 mL vessel and one 30 mL vessel. Both members of each set are subjected to the same reaction conditions as outlined below.

In the first set of vessels is placed N,N'-bis Boc-(L)-lysine (*ca.* 10 equiv.) as a solution in DMF (60 mL in the larger vessel, 15 mL in the smaller). HOBr (*ca.* 15 equiv.) is added and the resin agitated for 15 min. 15 DIC (*ca.* 10 equiv.) is added and the resin agitated for 4 hr. The resin is washed with DCM (2X) and then treated with TFA (30% solution in DCM) (1.5 hrs.). The resin is then washed with DCM (2X) and treated with 10% triethylamine in DMF (2X, 30 min. each). The resin is washed with alternating DCM and methanol (5X each) and then 20 with EtOAc (2X).

In the second set of vessels is placed N- α -Fmoc-N- ω -Pmc-(L)-arginine (*ca.* 10 equiv.) as a solution in DMF (60 mL in the larger vessel, 15 mL in the smaller). HOBr (*ca.* 15 equiv.) is added and the resin agitated for 15 min.. DIC (*ca.* 10 equiv.) is added and the resin 25 agitated for 4 hr. The resin is washed with DCM (2X) and then treated with TFA (50% solution in DCM) (1.5 hrs.). The resin is then washed with DCM (2X) and treated with 50% piperidine in DMF (2X, 30 min. each). The resin is washed with alternating DCM and methanol (5X each) and then with EtOAc (2X).

30 In the third set of vessels is placed DCM (60 mL in the larger vessel, 15 mL in the smaller). N,N-di-n-propyl-N'-cyano-ethylthioformamidine (*ca.* 15 equiv.) is added, followed by triethylamine (*ca.* 20 equiv.) and the resin agitated for 12 hrs. The resin is washed with alternating DCM and MeOH (5X each) and then 35 with EtOAc (2X).



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In the fourth set of vessels is placed absolute ethanol (60 mL in the larger vessel, 15 mL in the smaller). Methyl isocyanate (*ca.* 15 equiv.) is added and the resin agitated for 12 hr. The resin is washed with alternating DCM and methanol (5X each) and then with 5 EtOAc (2X).

In the fifth set of vessels is placed absolute ethanol (60 mL in the larger vessel, 15 mL in the smaller). Methyl isothiocyanate (*ca.* 15 equiv.) is added and the resin agitated for 12 hr. The resin is washed with alternating DCM and methanol (5X each) and then with 10 EtOAc (2X).

In the sixth set of vessels is placed absolute ethanol (60 mL in the larger vessel, 15 mL in the smaller). Phenyl isocyanate (*ca.* 15 equiv.) is added and the resin agitated for 12 hr. The resin is washed 15 with alternating DCM and methanol (5X each) and then with EtOAc (2X).

In the seventh set of vessels is placed absolute ethanol (60 mL in the larger vessel, 15 mL in the smaller). Phenyl isothiocyanate (*ca.* 15 equiv.) is added and the resin agitated for 12 hr. The resin is washed 20 with alternating DCM and methanol (5X each) and then with EtOAc (2X).

In the eighth set of vessels is placed DCM (60 mL in the larger vessel, 15 mL in the smaller) and 2,6-lutidine (*ca.* 20 equiv.). Isopropyl chloroformate (*ca.* 15 equiv.) is added and the resin agitated 25 for 4 hr. The resin is washed with alternating DCM and methanol (5X each) and then with EtOAc (2X).

In the ninth set of vessels is placed DCM (60 mL in the larger vessel, 15 mL in the smaller) and triethylamine (15 equiv.). Isobutryl chloride (*ca.* 10 equiv.) is added and the resin agitated 30 for 4 hr. The resin is washed with alternating DCM and methanol (5X each) and then with EtOAc (2X).

In the tenth set of vessels is placed DCM (60 mL in the larger vessel, 15 mL in the smaller) and triethylamine (15 equiv.). Methanesulfonyl chloride (*ca.* 10 equiv.) is added and the resin agitated 35 for 4 hr. The resin is washed with alternating DCM and methanol (5X each) and then with EtOAc (2X).



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Table 2-1
 $(CH_2)_{1-6}R^{17}$ Reagents and Encoding Scheme

5	<p>1 Cl_5C_{11}</p>	<p>5 Cl_5C_7 Cl_5C_{11}</p>
10	<p>2 Cl_5C_8</p>	<p>6 Cl_5C_7 Cl_5C_8 OMe</p>
15	<p>3 Cl_5C_8 Cl_5C_{11}</p>	<p>7 Cl_5C_7 Cl_5C_8 Cl_5C_{11}</p>
20	<p>4 Cl_5C_7</p>	
25		

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Table 2-2
Substituted Hydroxyacetophenone Reagents

1		4	
2		5	
3		6	

Table 2-3
R⁴R⁵ Step 3 Reagents

1		2		3	
25					
30					

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Table 2-4
R⁴R⁵ Step 3 Alt. Reagents

1		5	
2		6	
3		7	
4			

15

Table 2-5
R⁸ Reagents

20		5	
25		6	
30		7	

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Table 2-6
(CH₂)₁₋₆R¹⁴ Reagents

5	H ₃ C-NH ₂ 1	5	
10	 2	6	
15	MeO 3	7	
20	 4		

Table 2-7
R⁶/R⁷ Reagents

25	1 BF ₃ OEt ₂	2 NaBH ₄	3 No Reaction
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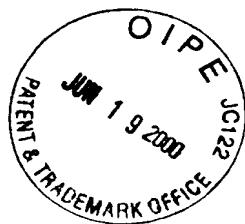
Table 2-8
R¹³ Reagents

5	1	6
10	2	7
15	3	8
	4 Me-N=C=O	9
	5 Me-N=C=S	10

20

25

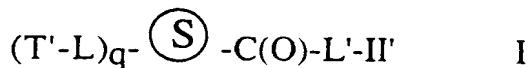
30



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WHAT IS CLAIMED IS:

1. A compound of the formula:

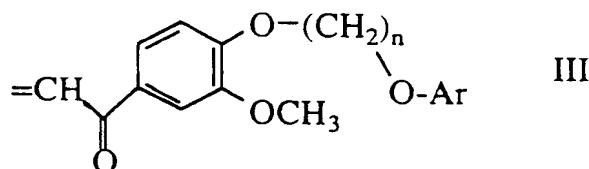


wherein:

5 \textcircled{S} is a solid support;
 T'-L- is an identifier residue;
 -L'-II' is a ligand/linker residue; and
 q is 3-30.

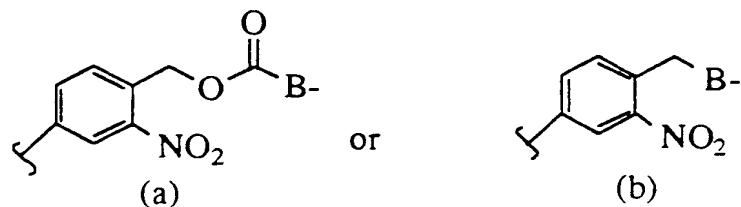
2. A compound of Claim 1 wherein:

10 T'-L- is of the Formula:



wherein n = 3-12 when Ar is pentachlorophenyl and
 n = 3-6 when Ar is 2,4,6-trichlorophenyl;

15 q is 4-12; and
 -L'- is

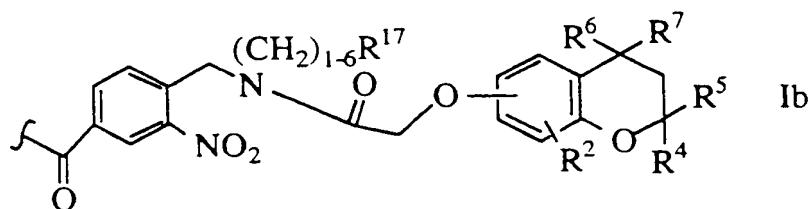
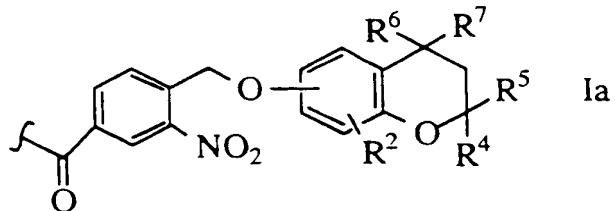


wherein the left-hand bond as shown is the point of attachment to the solid support and the right hand bond is the point of attachment to the ligand, and B is O or $N(CH_2)_{1-6}R^{17}$, with the proviso that in (b) when B is $N(CH_2)_{1-6}R^{17}$, the ligand is attached to B through a carbonyl group.

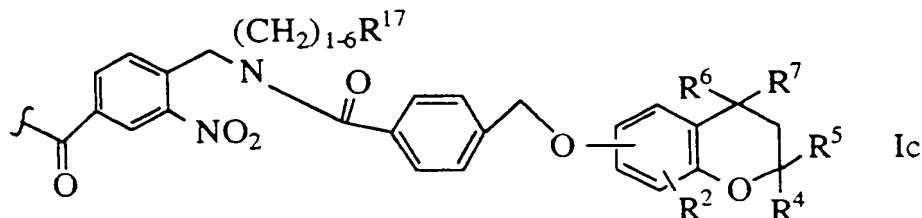


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3. A compound of Claim 1 wherein -C(O)-L'-II' is:

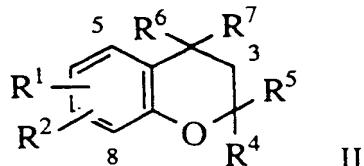


or



4. A compound of the formula:

5.



wherein:

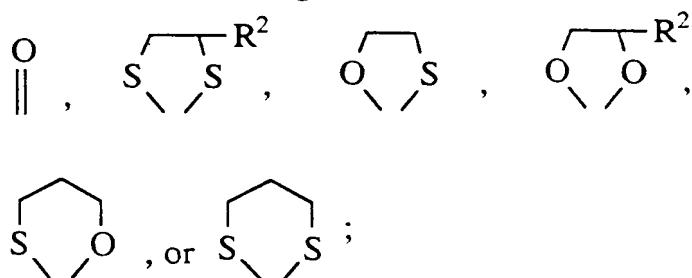
R¹ is OH, O(CH₂)₁₋₂OH, OCH₂CO₂H, CO₂H,O-Z-C(O)NH(CH₂)₁₋₆R¹⁷, orOCH₂-4-Phe-C(O)NH(CH₂)₁₋₆R¹⁷;10 R² is H or lower alkyl;R³ is H, alkyl, aryl, or arylalkyl;R⁴ and R⁵ is each independently H, lower alkyl, or substituted lower alkyl where the substituents are 1-3 alkoxy, aryl,



5

substituted aryl, carboalkoxy, carboxamido, or diloweralkylamido; or R⁴ and R⁵ taken together are -(CH₂)_n-, -(CH₂)₂-O-(CH₂)₂-, -CH₂-O-(CH₂)₃-, -(CH₂)₂-NR⁸-(CH₂)₂-, -CH₂-NR⁸-(CH₂)_m-, -(CH₂)₂CH(NHR⁸)(CH₂)₂-, -(CH₂)₂-S(O)O-₂-(CH₂)₂-, or -CH₂CH(N-loweralkyl)(CH₂)₂CHCH₂-;

one of R⁶ and R⁷ is H and the other is H, OH, or N(CH₂)₁₋₆R¹⁴R¹⁵; or R⁶ and R⁷ taken together are



10 R⁸ is H, COOR⁹, CONHR¹⁰, CSNHR¹¹, COR¹², SO₂R¹³, lower alkyl, aryl lower alkyl, heteroaryl, or heteroaryl lower alkyl, wherein aryl is optionally substituted with 1-3 substituents selected from lower alkyl, lower alkoxy, halo, CN, NH₂, COOH, CONH₂, carboalkoxy, and mono- or di-lower alkylamino and wherein heteroaryl is a mono- or bicyclic heteroaromatic ring system of 5 to 10 members including 1 to 3 heteroatoms selected from O, N, and S and 0-3 substituents selected from halo, amino, cyano, lower alkyl, carboalkoxy, CONH₂, and S-lower alkyl;

15

20 R⁹ is lower alkyl, aryl, aryl lower alkyl, heteroaryl, aryl substituted by 1-3 substituents selected from alkyl, alkenyl, alkoxy, methylene dioxy, and halo, or a 5 to 6-membered heterocyclic ring wherein the hetero atom is O or N, wherein heteroaryl is a heteroaromatic ring of 5 to 6 members including 1 to 2 heteroatoms selected from O, N, and S and 0-2 substituents selected from lower alkyl, dialkylamino, lower alkoxy, and halo;

25



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R¹⁰ and R¹¹ is each independently lower alkyl, aryl, aryl lower alkyl, or aryl substituted by 1-3 substituents selected from lower alkyl, halo, alkoxy, and haloalkyl;

5 R¹² is lower alkyl, aryl, heteroaryl, aryl lower alkyl, heteroaryl lower alkyl, a 5- or 6-membered heterocyclic ring containing 1-2 heteroatoms selected from O, S, and N, a 5- or 6-membered heterocyclic ring containing 1-2 heteroatoms selected from O, S, and N lower alkyl, or aryl substituted with 1-3 substituents selected from lower

10 alkyl, alkoxy, halo, sulfamoyl, lower alkyl sulfamoyl, cyano, and phenyl;

R¹³ is lower alkyl, aryl, or aryl substituted with 1-3 substituents selected from lower alkyl, alkoxy, halo, CN, and haloalkyl;

15 R¹⁴ is H; alkyl substituted by 1-3 alkoxy, S-loweralkyl, sulfamoyl, halo, alkylsulphonamido, or arylsulphonamido; alkenyl; alkynyl; aryl; substituted aryl; heteroaryl; substituted heteroaryl; heterocycloalkyl; -CH₂NR¹⁶C(O)R¹⁶; -C(O)NR¹⁶R¹⁶; -CH₂OC(O)R¹⁶; or -CH₂SC(O)R¹⁶;

20 R¹⁵ is H, alkyl, -C(O)X, -C(S)X, or -C(NCN)NR³R³;

R¹⁶ is lower alkyl, substituted lower alkyl, aryl, or substituted aryl;

25 R¹⁷ is H; alkyl substituted by 1-3 alkoxy, S-loweralkyl, sulfamoyl, halo, alkylsulphonamido, or arylsulphonamido; alkenyl; alkynyl; aryl; substituted aryl; heteroaryl; substituted heteroaryl; heterocycloalkyl; -CH₂NR¹⁶C(O)R¹⁶; -C(O)NR¹⁶R¹⁶; -CH₂OC(O)R¹⁶; or -CH₂SC(O)R¹⁶;

X is alkyl, aryl, arylalkyl, O-loweralkyl, or NR³R³

30 Z is -(CH₂)₁₋₆, optionally substituted with 1-3 lower alkyl; CHR²; Phe-CH₂-, where Phe is optionally mono-substituted with halogen, lower alkyl, or alkoxy; or heteroarylene-(CH₂)-;

m is 2 or 3;

35 n is 4-9;

or a pharmaceutically acceptable salt thereof.



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5. A compound of Claim 3 wherein R¹² is sulfamoylphenyl.

6. A compound of Claim 3 wherein R¹² is p-sulfamoylphenyl.

5 R¹ is 7. A compound of Claim 4 wherein:
 OH, OCH₂C(O)NH(CH₂)₁₋₆R¹⁴, or OCH₂-4-Phe-
 C(O)NH(CH₂)₁₋₆R¹⁴;

10 R² is H or lower alkyl;
 R⁴ and R⁵ is each lower alkyl; or R⁴ and R⁵ taken together are
 -(CH₂)₅-, -(CH₂)₂-O-(CH₂)₂-, -(CH₂)₂-NR⁸-(CH₂)₂-,
 -(CH₂)₂-CH(NHR⁸)(CH₂)₂-, -(CH₂)₂-S-(CH₂)₂-, or
 -CH₂CH(NCH₃)(CH₂)₂CHCH₂-;

15 R⁶/R⁷ are H/OH, =O, or -S(CH₂)₂S-;
 R⁸ is H, COOR⁹, CONHR¹⁰, CSNHR¹¹, COR¹², SO₂R¹³, .
 lower alkyl, aryl lower alkyl, heteroaryl wherein the ring
 members include 1 to 3 N atoms and the substituents are
 halo or amino, heteroaryl lower alkyl wherein heteroaryl
 is 6-membered and the heteroatoms are N, or aryl lower
 alkyl substituted with 1 substituent selected from lower
 alkyl, alkoxy, and halo;

20 R⁹ is lower alkyl, aryl lower alkyl, aryl, tetrahydrofuranyl,
 tetrahydropyranyl, or aryl substituted by 1 to 2
 substituents selected from lower alkyl, alkenyl, alkoxy,
 methylene dioxy, and halo;

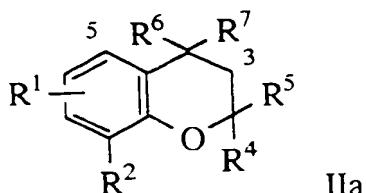
25 R¹⁰ and R¹¹ is each independently aryl, aryl lower alkyl, or aryl
 substituted by 1 substituent selected from lower alkyl, halo,
 alkoxy, trifluoromethyl, and pentafluoroethyl;

30 R¹² is lower alkyl, aryl, aryl lower alkyl, heteroaryl lower
 alkyl wherein the heteroatoms are N, a 5- or 6-membered
 heterocyclic ring containing 1-2 heteroatoms selected from
 S and N lower alkyl, or aryl substituted with 1 substituent
 selected from lower alkyl, alkoxy, halo, sulfamoyl,
 cyano, or phenyl;

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R^{13} is lower alkyl, aryl, or aryl substituted with 1 substituent selected from lower alkyl, alkoxy, and halo; or a pharmaceutically acceptable salt thereof.

8. A compound of Claim 4 of the formula:



5

IIa

wherein:

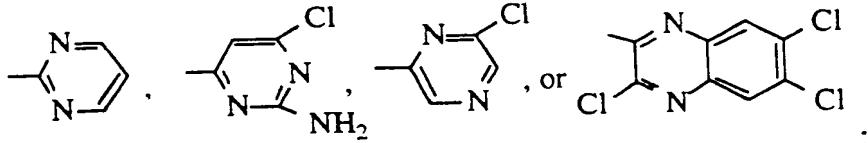
R^1 is 6- or 7-OH;

R^2 is H or lower alkyl;

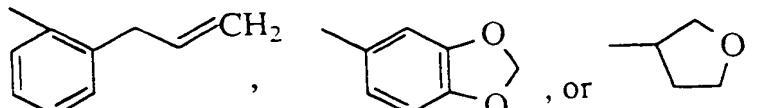
R^4 and R^5 is each methyl; or R^4 and R^5 taken together are $-(CH_2)_5-$,
10 $-(CH_2)_2-O-(CH_2)_2-$, $-(CH_2)_2-NR^8-(CH_2)_2-$,
 $-CH_2-NR^8-(CH_2)_3-$, $-CH_2-NR^8-(CH_2)_2-$, or $-(CH_2)_2-$
 $CH(NHR^8)(CH_2)_2-$;

one of R^6 and R^7 is H and the other is OH or R^6 and R^7 taken together
are $=O$ or $-S(CH_2)_2S-$;

15 R^8 is H, $COOR^9$, $CONHR^{10}$, $CSNHR^{11}$, COR^{12} , SO_2R^{13} ,
benzyl, $-CH_2-Ph-4-F$, $-CH_2-Ph-4-OCH_3$, $-CH_2-4-Py$,
n-butyl, $-CH_2-c\text{-}propyl$,

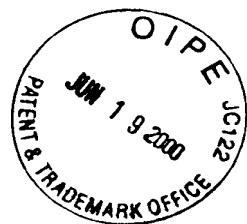


R^9 is i-propyl, phenyl, phenethyl, t-butyl,

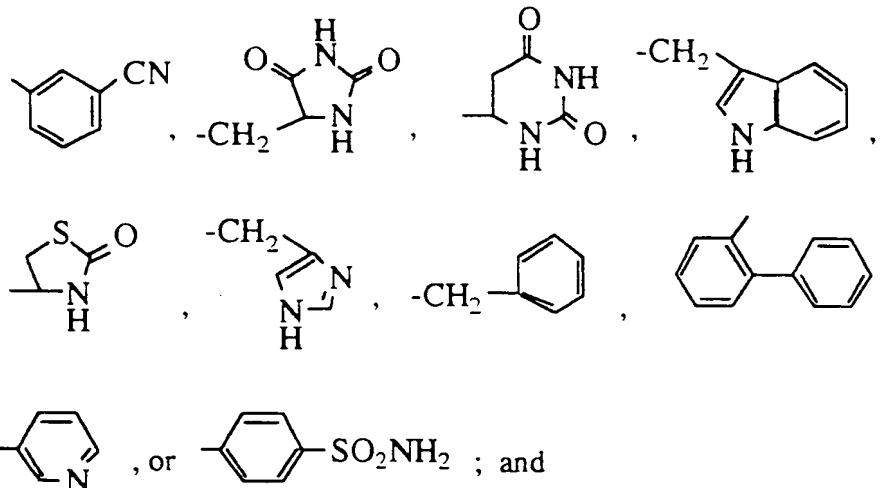


20

R^{10} phenyl, p-chlorophenyl, or p-trifluoromethylphenyl;
 R^{11} is phenyl, benzyl, or 1-naphthyl;

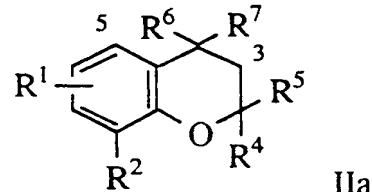


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 R^{12} is

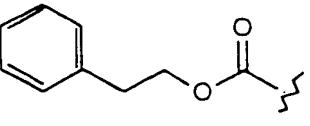
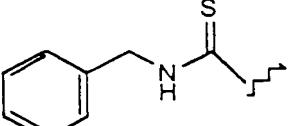
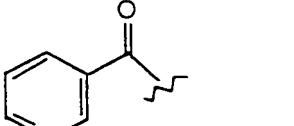
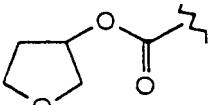
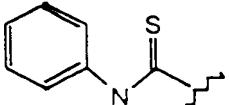
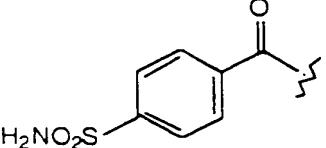
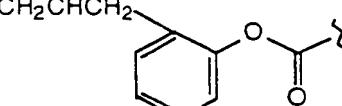
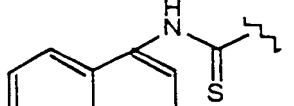
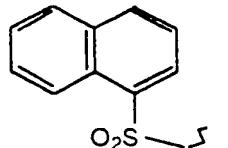
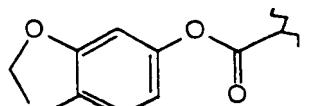
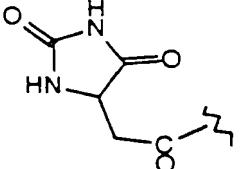
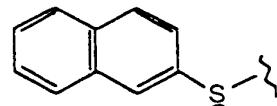
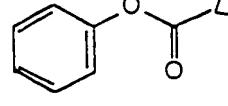
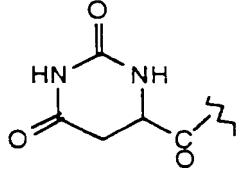
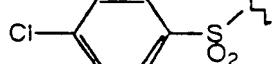
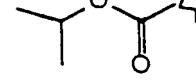
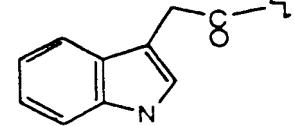
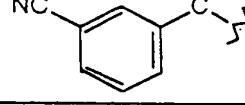
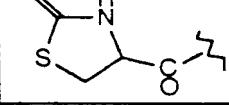
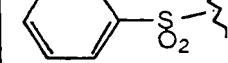
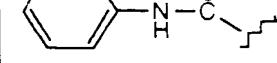
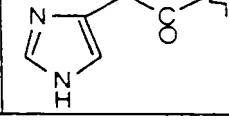
R^{13} is 1- or 2-naphthyl, phenyl, 4-chlorophenyl, 4-methylphenyl, 4-t-butylphenyl, n-butyl, or i-propyl;
 5 or a pharmaceutically acceptable salt thereof.

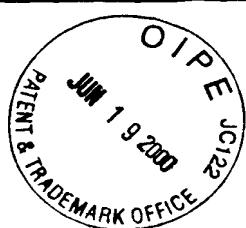
9. A compound of Claim 4 of the formula:



wherein:

10 R^1 is 6- or 7-OH when R^2 is H;
 R^1 is 7-OH when R^2 is CH_3 ;
 R^4 and R^5 is each methyl; or R^4 and R^5 taken together are $-(CH_2)_5-$,
 $-(CH_2)_2-O-(CH_2)_2-$, $-(CH_2)_2-NR^8-(CH_2)_2-$,
 $-CH_2-NR^8-(CH_2)_3-$, $-CH_2-NR^8-(CH_2)_2-$, or $-(CH_2)_2-$
 15 $CH(NHR^8)(CH_2)_2-$;
 one of R^6 and R^7 is H and the other is OH or R^6 and R^7 taken together
 are =O or $-S(CH_2)_2S-$; and
 R^8 is



<chem>Clc1ccc(NC(=O)C=C)c1</chem>	<chem>Cc1ccccc1CC=C</chem>	<chem>CC(C)CS(=O)(=O)C=C</chem>
<chem>F3Cc1ccc(NC(=O)C=C)c1</chem>	<chem>Cc1ccc(cc1)-c2ccccc2C(=O)C=C</chem>	<chem>CC(C)SC(=O)(=O)c1ccc(cc1)C(C)=C</chem>
<chem>CN1=CC=CC=C1C=C</chem>	<chem>CC(C)OCc1ccc(cc1)C=C</chem>	<chem>CC(C)Nc1nc(Cl)cc2cc(C=C)nc12</chem>
<chem>Cc1ccccc1C=C</chem>	<chem>CN1=CC=CC=C1ClC=C</chem>	<chem>Cc1ccccc1C=C</chem>
<chem>Clc1cc(Cl)c2cc3c(Cl)nc(OCC)cc3cc12</chem>	<chem>CCCCC=C</chem>	<chem>FCc1ccc(cc1)C=C</chem>
<chem>C1CC1</chem>	<chem>CC(C)OC(=O)C(C)=C</chem>	or H.

10. A compound of Claim 4 of the formula



wherein:

30 R¹ is 6- or 7-OCH₂C(O)NH(CH₂)₁₋₆R¹⁷, or 6- or 7-OCH₂-4-Phe-C(O)NH(CH₂)₁₋₆R¹⁷ when R² is H;

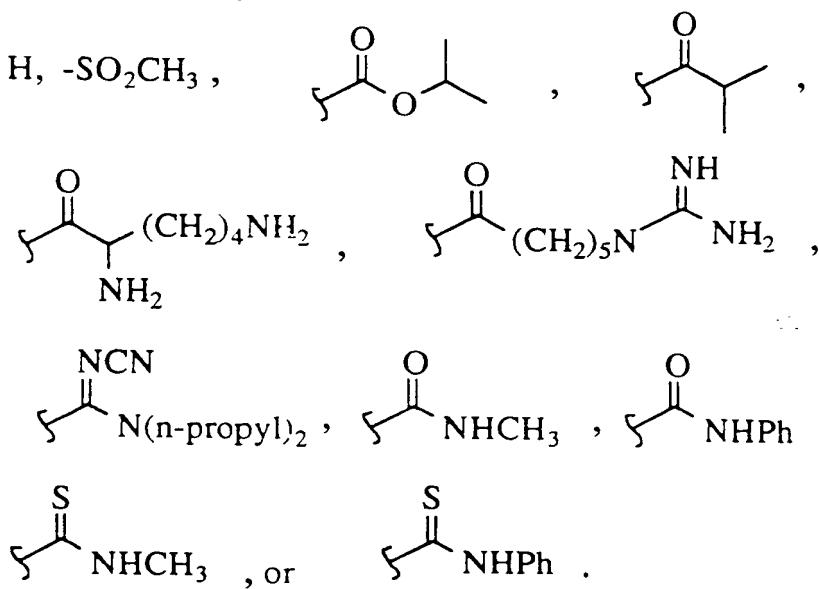
R¹ is 7-OCH₂C(O)NH(CH₂)₁₋₆R¹⁷, or 7-OCH₂-4-Phe-C(O)NH(CH₂)₁₋₆R¹⁷ when R² is CH₃;



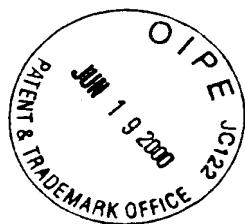
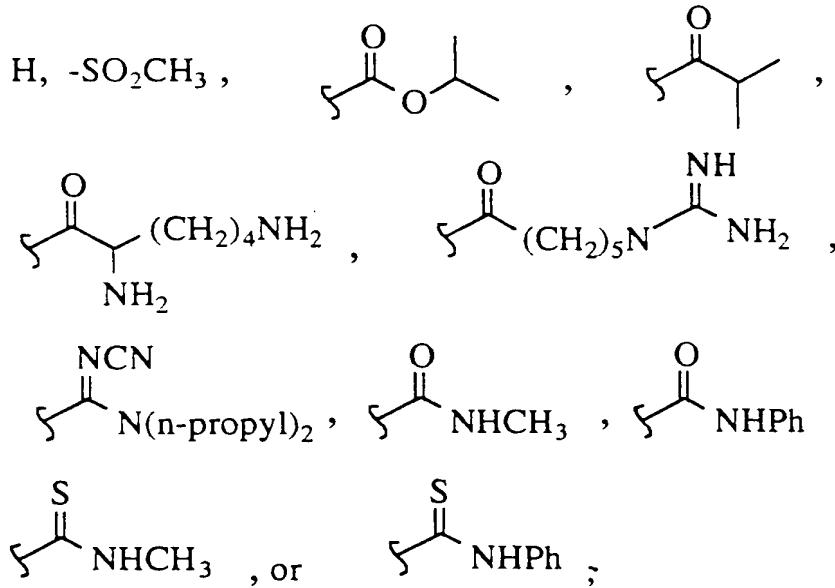
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R^4 and R^5 is each methyl; or R^4 and R^5 taken together are $-(CH_2)_5-$,
 $-(CH_2)_2-O-(CH_2)_2-$, $-(CH_2)_2-NR^8-(CH_2)_2-$,
 $-(CH_2)_2-CH(NHR^8)(CH_2)_2-$, $-(CH_2)_2-S-(CH_2)_2-$, or
 $-CH_2CH(NCH_3)(CH_2)_2CHCH_2-$;

5 or R⁴ is methyl and R⁵ is CH₂OCH₃ or -(CH₂)₃N(Et)₂;
one of R⁶ and R⁷ is H and the other is OH; or R⁶ and R⁷ taken together
are =O or -S(CH₂)₂S-; or one of R⁶ and R⁷ is H and the
other is NAB, where A is methyl, 2-methoxyethyl,
2-phenylethyl, 4-methoxybenzyl, 2-tetrahydro-
furanylmethyl, 2(3,4-dimethoxyphenyl)ethyl, or
10 2,2-diphenylethyl and B is



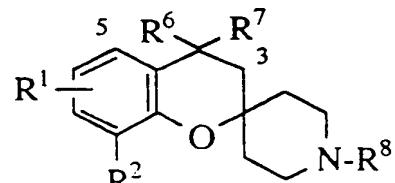
15. R⁸ is H, CONHCH₃, SO₂Ph, (CH₂)₃CH₃, CO(CH₂)₂CH₃, benzyl, -C(O)-(4-Phe)-SO₂NH₂, or
;

R¹³ is

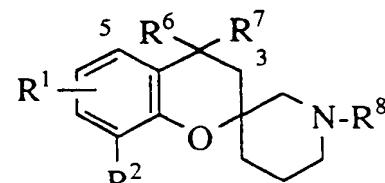
(CH₂)₁₋₆R¹⁴ is methyl, n-butyl, 3-methoxy-n-propyl, CH₂-c-propyl, or -(CH₂)₁₋₃-phenyl; and

5 (CH₂)₁₋₆R¹⁷ is methyl, 2-methoxyethyl, 2-phenylethyl, 4-methoxybenzyl, methyl-2-tetrahydrofuryl, 2(3,4-dimethoxyphenyl)ethyl, or 2,2-diphenylethyl; or a pharmaceutically acceptable salt thereof.

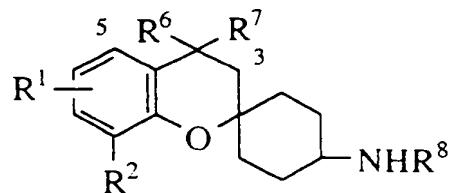
10 11. A compound of Claim 4 of the formulae IIb, IIc, and IIId:



IIb



IIc



IIId



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wherein:

R¹ is 6- or 7-OH, 6- or 7-OCH₂C(O)NH(CH₂)₁₋₆R¹⁷, or
6- or 7-OCH₂-4-Phe-C(O)NH(CH₂)₁₋₆R¹⁷;

R² is H or CH₃;

R⁸ is -CO-Ph-p-SO₂NH₂; and

R⁶ and R⁷ together are =O or -SCH₂CH₂S-.

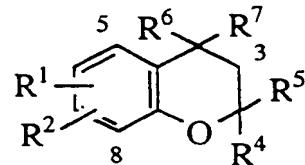
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12. A compound of Claim 11 wherein the substituents are as follows:

	Formula IIb	Formula IIc	Formula IIId		
10	R ¹ 7-OH	6-OH	6-OH	6-OH	7-OH
	R ² H	H	H	H	CH ₃
	R ⁶ /R ⁷ -O-	-SCH ₂ CH ₂ S-	-O-	-SCH ₂ CH ₂ S-	-SCH ₂ CH ₂ S-

15

13. A compound of Claim 4 of the formula:



20

wherein the substituents are as follows:

R ¹	R ²	R ⁴	R ⁵	R ⁶	R ⁷
6-OH	8-CH ₃	C ₂ H ₅	C ₂ H ₅	OH	H
7-OH	8-CH ₃	CH ₃	CH ₃	H	OH
5-OH	7-CH ₂ H ₅	H	CH ₂ H ₅	NH ₂	H
6-O-(CH ₂) ₂ OH	H	C ₃ H ₇	CH ₃	=O	
7-OCH ₂ CO ₂ H	H		-(CH ₂) ₄ -	H	morpholino
8-O-(CH ₂) ₂ OH	H		-(CH ₂) ₅ -	N(CH ₃) ₂	H
6-CO ₂ H	8-CH ₃		-(CH ₂) ₆ -	-S(CH ₂) ₂ S-	
6-OH	H		-(CH ₂) ₂ O(CH ₂) ₂ -	=O	
7-OH	8-CH ₃	CH ₃	CH ₃	-S(CH ₂) ₂ S-	
6-OH	H		-(CH ₂) ₅ -	=O	

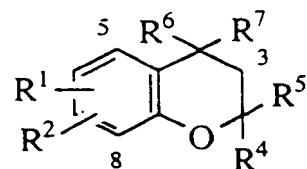
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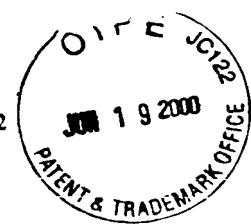
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14. A compound of Claim 4 of the formula:



5 wherein the substituents are as follows:

	R ¹	R ²	R ³ /R ⁴	R ⁶	R ⁷	R ⁸	
10	6-OH	H	-(CH ₂) ₂ NR ⁸ - (CH ₂) ₂ -	OH	H	-CONH-Ph-4-CF ₃	
15	7-OH	8-CH ₃	-CH ₂ NR ⁸ - (CH ₂) ₃ -	-N [cyclic]	SO ₂	H	-SO ₂ -2-Naph
20	5-O(CH ₂) ₂ OH	7-C ₂ H ₅	-(CH ₂) ₂ NR ⁸ - CH ₂ -	-N [cyclic]	H	-CSNH-Ph	
25	6-OH	H	-(CH ₂) ₂ NR ⁸ - (CH ₂) ₂ -	=O		-CO-Ph-4-SO ₂ NH ₂	
30	7-OH	H	-(CH ₂) ₂ CH- (NR ⁸)(CH ₂) ₂ -	-S(CH ₂) ₂ S-		-CO-Ph-4-SO ₂ NH ₂	
	6-OH	H	-(CH ₂) ₂ NR ⁸ - (CH ₂) ₂ -	=O		-COCH ₂ Ph	
	6-OH	H	-(CH ₂) ₂ NR ⁸ - CH ₂ -	-S(CH ₂) ₂ S-		-CO ₂ -2-Py	
	7-OH	8-CH ₃	-(CH ₂) ₂ NR ⁸ - (CH ₂) ₂ -	-S(CH ₂) ₂ S-		-CO-Ph-4-SO ₂ NH ₂	
	6-OH	H	-(CH ₂) ₂ NR ⁸ - CH ₂ -	-S(CH ₂) ₂ S-		-CO-Ph-4-SO ₂ NH ₂	
	7-OH	H	-(CH ₂) ₂ NR ⁸ - (CH ₂) ₂ -	=O		-CO-Ph-4-SO ₂ NH ₂	



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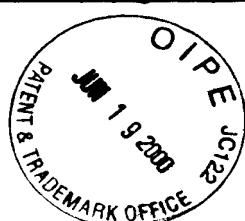
	6-OH	H	-(CH ₂) ₂ NR ⁸⁻ (CH ₂) ₂ -	OH	H	CONH-Ph-4-CF ₃
5	7-OH	8-CH ₃	-(CH ₂) ₂ NR ⁸⁻ CH ₂ -	N(CH ₃) ₂	H	-SO ₂ -2-Naph
	5-O(CH ₂) ₂ OH	7-C ₂ H ₅	-(CH ₂) ₂ NR ⁸⁻ CH ₂ -	-SCH ₂ CH- (CH ₃)S-	H	-CSNH-Ph
10	6-OH	H	-(CH ₂) ₂ NR ⁸⁻ (CH ₂) ₂ -	=O		-CO-Ph-4-SO ₂ NH ₂
	7-OH	H	-(CH ₂) ₂ NR ⁸⁻ (CH ₂) ₂ -	-S(CH ₂) ₂ S-		-CO-Ph-4-SO ₂ NH ₂
15	6-OH	H	-(CH ₂) ₂ NR ⁸⁻ (CH ₂) ₂ -	=O		COCH ₂ Ph
	6-OH	H	-(CH ₂) ₂ NR ⁸⁻ CH ₂ -	-S(CH ₂) ₂ S-		-CO ₂ -2-Py
20	7-OH	8-CH ₃	-(CH ₂) ₂ NR ⁸⁻ (CH ₂) ₂ -	-S(CH ₂) ₂ S-		-CO-Ph-4-SO ₂ NH ₂
	6-OH	H	-(CH ₂) ₂ NR ⁸⁻ CH ₂ -	-S(CH ₂) ₂ S-		-CO-Ph-4-SO ₂ NH ₂
25	7-OH	H	-(CH ₂) ₂ NR ⁸⁻ (CH ₂) ₂ -	=O		-CO-Ph-4-SO ₂ NH ₂

25

15. A pharmaceutical composition comprising a therapeutically effective amount of a compound of Claim 4 and a pharmaceutically acceptable carrier.

30

16. A pharmaceutical composition comprising a therapeutically effective amount of a compound of Claim 9 and a pharmaceutically acceptable carrier.



17. A pharmaceutical composition comprising a therapeutically effective amount of a compound of Claim 10 and a pharmaceutically acceptable carrier.
18. A pharmaceutical composition for inhibiting carbonic anhydrase in a mammal comprising a therapeutically effective amount of a compound of Claim 11 and a pharmaceutically acceptable carrier.
19. A method of inhibiting carbonic anhydrase isozymes in a mammal which comprises administering to said mammal an effective amount of a compound of Claim 11.
- 10 20. A method of treating glaucoma in a mammal which comprises administering to a mammal in need of such treatment an effective amount of a compound of Claim 11.
- 15 21. A method of identifying a ligand having a desired characteristic which comprises synthesizing a combinatorial library of Claim 1 and testing the compounds in said library in an assay which identifies compounds having the desired characteristic.
22. A method of of Claim 21 wherein the compounds in said library are those wherein -C(O)-L'-II' is of the formula Ia.
- 20 23. A method of Claim 21 further comprising determining the structure of any ligand so identified.
24. A method of Claim 21 wherein said characteristic is carbonic anhydrase inhibition.
- 25 25. A method for identifying compounds that are inhibitors of carbonic anhydrase which comprises preparing a mixture of 20-300 pmol test compound and aqueous solutions (total volume: 25-100 μ L) of 0.03-1.2 μ M carbonic anhydrase and 0.04-1.6 μ M dansylamide, exposing said mixture to U.V. (preferably 274 nm) light, and determining the amount of emitted U.V. (preferably 454 nm) light.
- 30 26. A method of Claim 25 wherein the total volume is about 50 μ L, the carbonic anhydrase concentration is about 0.3 μ M, the



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dansylamide concentration is about 0.6 μM , the mixture is exposed to 274 nm U.V. light, and the emitted U.V. light is 454 nm.

27. A method for identifying compounds that are enzyme inhibitors which is a lawn assay which comprises contacting a first layer which is a colloidal matrix containing enzyme, which matrix has embedded therein a mono-layer of solid supports with attached ligands, with a second layer which contains a substrate which can be monitored photometrically during its enzymic conversion to product, eluting said ligands by exposure to U.V. light, and detecting zones of inhibition in said first layer produced thereby.

28. A method of Claim 27 wherein said first layer is an agarose matrix containing bovine carbonic anhydrase and said second layer is a fluorescein diacetate-containing layer of agarose.

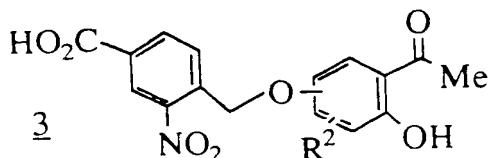
29. A method of identifying a ligand having a desired characteristic which comprises synthesizing a combinatorial library of Claim 1, detaching the ligands from the solid supports in said library, and testing said library of ligands in an assay which identifies compounds having the desired characteristic.

30. A method of Claim 29 further comprising determining the structure of any ligand so identified.

31. The use of divinylbenzene-cross-linked, polyethyleneglycol-grafted polystyrene beads as the solid supports for constructing combinatorial libraries of Claim 1.

32. A method of Claim 31 wherein the ligand is detached from said solid supports by photolysis.

33. A process for preparing a compound of the formula:



where R^2 is H or lower alkyl;